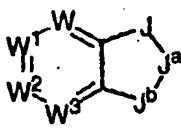




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(21) International Application Number: PCT/US98/18729 (22) International Filing Date: 8 September 1998 (08.09.98) (30) Priority Data: 60/058,288 9 September 1997 (09.09.97) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; WR-1ST18, 974 Centre Road, Wilmington, DE 19807 (US). (72) Inventors: HAN, Qi; 2609 Marhill Drive, Wilmington, DE 19810 (US). DOMINGUEZ, Celia; 963 Cedar Cliff Court, Westlake Village, CA 91320 (US). AMPARO, Eugene, C.; 416 Corner Ketch Lyndell, Downingtown, PA 19335 (US). PARK, Jeongsong, M.; 241, Cornwell Drive, Bear, DE 19701 (US). QUAN, Mimi, L.; 113 Venus Drive, Newark, DE 19711 (US). ROSSI, Karen, A.; 120A Emery Court, Newark, DE 19711 (US). (74) Agent: VANCE, David, H.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).			(81) Designated States: AU, CA, IL, JP, MX, NZ, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: BENZIMIDAZOLINONES, BENZOXAZOLINONES, BENZOPIPERAZINONES, INDANONES, AND DERIVATIVES THEREOF AS INHIBITORS OF FACTOR XA			
<div style="text-align: center;"> (I)</div>			
(57) Abstract The present application describes inhibitors of factor Xa of formula (I) or pharmaceutically acceptable salt forms thereof, wherein W, W ¹ , W ² and W ³ may be N or C and J, J ^a , and J ^b combine to form a substituted carbocycle or heterocycle.			

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TITLE

Benzimidazolinones, Benzoxazolinones, Benzopiperazinones,
Indanones, and Derivatives Thereof as Inhibitors of Factor Xa

5

FIELD OF THE INVENTION

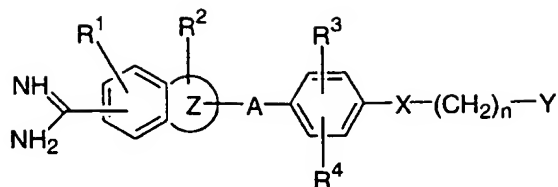
This invention relates generally to novel
benzimidazolinones, benzoxazolinones, benzopiperazinones,
indanones, and derivatives thereof as inhibitors of factor Xa,
10 pharmaceutical compositions containing the same, and methods
of using the same as anticoagulant agents for treatment and
prevention of thromboembolic disorders.

BACKGROUND OF THE INVENTION

15 Activated factor Xa, whose major practical role is the
generation of thrombin by the limited proteolysis of
prothrombin, holds a central position that links the intrinsic
and extrinsic activation mechanisms in the final common
pathway of blood coagulation. The generation of thrombin, the
20 final serine protease in the pathway to generate a fibrin
clot, from its precursor is amplified by formation of
prothrombinase complex (factor Xa, factor V, Ca^{2+} and
phospholipid). Since it is calculated that one molecule of
factor Xa can generate 138 molecules of thrombin (Elodi, S.,
25 Varadi, K.: *Optimization of conditions for the catalytic
effect of the factor IXa-factor VIII Complex: Probable role of
the complex in the amplification of blood coagulation.*
Thromb. Res. **1979**, 15, 617-629), inhibition of factor Xa may
be more efficient than inactivation of thrombin in
30 interrupting the blood coagulation system.

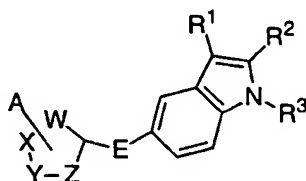
Therefore, efficacious and specific inhibitors of factor
Xa are needed as potentially valuable therapeutic agents for
the treatment of thromboembolic disorders. It is thus
desirable to discover new factor Xa inhibitors.

35 EP 0,540,051 and JP 06227971 describe a series of
compounds useful as factor Xa inhibitors or to treat influenza
based on the formula:



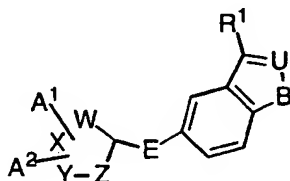
wherein A is an alkylene linker optionally substituted X is a bond, O, S, or carbonyl, n is 0-4, and Y is an optionally substituted carbocycle or heterocycle. The core ring containing Z can be a variety of benzofused heterocycles. However, the present invention does not involve compounds containing these benzofused heterocycles.

Baker et al, in U.S. Patent No. 5,317,103, discuss 5-HT₁ agonists which are indole substituted five-membered heteroaromatic compounds of the formula:



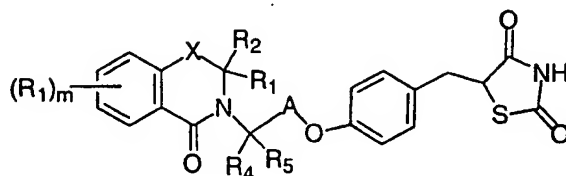
wherein R¹ may be pyrrolidine or piperidine and A may be a basic group including amino and amidino. Baker et al, however, do not appear to describe heterocycles which are part of the present invention.

Baker et al, in WO 94/02477, discuss 5-HT₁ agonists which are imidazoles, triazoles, or tetrazoles of the formula:



wherein R¹ represents a nitrogen containing ring system or a nitrogen substituted cyclobutane, and A may be a basic group including amino and amidino. But, the presently claimed invention doesn't relate to the heterocyclic cores of Baker et al.

EP 787,727 illustrates benzyl-thiazolidin-2,4-diones of the formula:



5 which are useful as hypoglycemic agents. However, these type
of compounds are outside of the present Xa inhibitors.

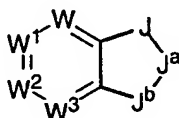
SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to
10 provide novel inhibitors of factor Xa or pharmaceutically
acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

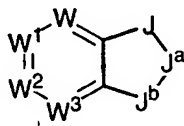


I

or pharmaceutically acceptable salt forms thereof, wherein W,
30 W¹, W², W³, J, J^a, and J^b are defined below, are effective
factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



I

or stereoisomer or pharmaceutically acceptable salt thereof, wherein;

one of W, W¹, W², and W³ is C-D and the remaining are C-R¹;

alternatively, W-W¹, W¹-W², or W²-W³ combine to form C(D^a)N and the remaining are C-R¹;

D is selected from CN, C(=NR⁷)NR⁸R⁹, NHC(=NR⁷)NR⁸R⁹, NR⁸CH(=NR⁷), C(O)NR⁸R⁹, and (CH₂)_tNR⁸R⁹;

D^a is NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, or C₁₋₃ alkoxy;

J is selected from N(Z-A-B) and CR(Z-A-B); and

J^a and J^b together are selected from CONHCR^eR^f, SO₂NHCR^eR^f, (CR^aR^b)_qSO₂NR^d, and (CR^aR^b)_bCOCO(CR^eR^f)_c, wherein b+c=0 or 1;

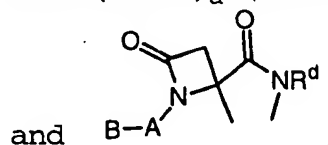
alternatively, J and J^a together are selected from CON(Z-A-B)(CR^cR^b)_q and N(Z-A-B)Q(R^cR^b)_a; and

J^b is selected from NR^d, O, and CR^eR^f;

Q is CO or CS;

alternatively, J, J^a and J^b together are selected from CR(Z-A-B)(CR^aR^b)_aQNR^d, CR(Z-A-B)(CR^aR^b)_dC(O)O, CR(Z-A-B)NHCOCR^eR^f, CR(Z-A-B)NHSO₂CR^eR^f, N(Z-A-B)(CR^aR^b)_aQNR^d, N(Z-A-B)(CR^aR^b)C(O)O,

$N(Z-A-B)SO_2(CR^cR^b)_aCR^eR^f$, $N(Z-A-B)SO_2(CR^cR^b)_aNR^d$,
 $CON(Z-A-B)CR^eR^f$, $CONR^b(CR^cR^b)_aN(Z-A-B)$,



5 R is selected from H, C₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, OH, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₄ alkyl, (CH₂)_tNR⁸R⁹, 5-6 membered aromatic heterocyclyl-C₁₋₄ alkyl, and aryl-C₁₋₄ alkyl, wherein the aromatic heterocyclyl and aryl groups are substituted with 0-1 R⁴;

10

R^a is selected from H, C₁₋₆ alkyl, C(O)R^{2b}, 5-6 membered aromatic heterocyclyl-C₁₋₄ alkyl, and aryl-C₁₋₄ alkyl, wherein the aromatic heterocyclyl and aryl groups are substituted with 0-1 R⁴;

15

R^b is H or C₁₋₂ alkyl;

20 R^c is selected from H, C₁₋₆ alkyl, C(O)R^{2b}, S(O)_pR^{2b}, BO₂H₂, 5-6 membered aromatic heterocyclyl-C₁₋₄ alkyl, and aryl-C₁₋₄ alkyl, wherein the aromatic heterocyclyl and aryl groups are substituted with 0-1 R⁴;

R^d is selected from H, OH, NH₂, C₁₋₂ alkyl, and C₁₋₂ alkyl-OH,

25 alternatively, R^c and R^d, when attached to adjacent atoms, together form a double bond;

R^e is selected from H, OH, NH₂, C₁₋₂ alkyl, and C₁₋₂ alkyl-OH,

30 alternatively, R^c and R^e, when attached to adjacent atoms, together form a double bond;

R^f is H or C₁₋₂ alkyl;

35 Z is selected from a bond, C₁₋₄ alkylene, (CH₂)_rO(CH₂)_r, (CH₂)_rNR³(CH₂)_r, (CH₂)_rC(O)(CH₂)_r, (CH₂)_rC(O)O(CH₂)_r,

$(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$,
 $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$,
 $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$,
 $(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$,
5 $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$, and
 $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, provided that Z does not form a
N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with the groups
to which it is attached;

10 R^1 , at each occurrence, is selected from H, F, Cl, Br, I,
 $(CF_2)_rCF_3$, OR^2 , NR^2R^{2a} , $C(O)R^{2b}$, $(CF_2)_rCO_2R^2$, $S(O)_2R^{2b}$,
 $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, C₃₋₆ carbocyclic residue
substituted with 0-2 R^4 , and 5-10 membered heterocyclic
15 system containing from 1-4 heteroatoms selected from the
group consisting of N, O, and S and substituted with 0-2
 R^4 ;

$R^{1'}$, at each occurrence, is selected from H, C₁₋₃ alkyl, F, Cl,
Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a} , $C(O)R^{2c}$,
20 $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$,
 $CH(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$,
 $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$,
 $NR^2SO_2R^{2b}$, C₃₋₆ carbocyclic residue substituted with 0-2
 R^{4b} , and 5-10 membered heterocyclic system containing from
25 1-4 heteroatoms selected from the group consisting of N,
O, and S substituted with 0-2 R^{4b} ;

$R^{1''}$, at each occurrence, is selected from H, $CH(CH_2OR^2)_2$,
 $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;
30

R^2 , at each occurrence, is selected from H, CF_3 , C₁₋₆ alkyl,
benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b} ,
and 5-6 membered heterocyclic system containing from 1-4
heteroatoms selected from the group consisting of N, O,
35 and S and substituted with 0-2 R^{4b} ;

R^{2a} , at each occurrence, is selected from H, CF_3 , C₁₋₆ alkyl,
benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b} ,

and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{4b};

5 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting
10 of N, O, and S;

R^{2b} is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4
15 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted
20 with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and
25 phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

30 A is selected from:
C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R⁴;

35 B is selected from: H, Y, and X-Y;

X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -C(=NR^{1"})-, -CR²(NR^{1"}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;

10

Y is selected from:

(CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,

C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, CH(=NR²)NR²R^{2a}, CH(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, C(O)NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, NCH₂R^{1"}, OCH₂R^{1"}, SCH₂R^{1"}, N(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and S(CH₂)₂(CH₂)_tR^{1'};

alternatively, one R⁴ is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR², (CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rNR²R^{2b}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(O)NH(CH₂)₂NR²R^{2a}, NR²C(O)NR²R^{2a}, CH(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, C(O)NHSO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, and (CF₂)_rCF₃;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

5 R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NH^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$,
10 $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl substituted with 0-2 R^6 , and benzyl substituted
15 with 0-2 R^6 ;

R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$,
20 $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7 , at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

30 R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$ -phenyl;

R^9 , at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$ -phenyl;

35 a, at each occurrence, is selected from 0, 1, and 2;

d, at each occurrence, is selected from 0 and 1;

- n, at each occurrence, is selected from 0, 1, 2, and 3;
- m, at each occurrence, is selected from 0, 1, and 2;
- 5 p, at each occurrence, is selected from 0, 1, and 2;
- q, at each occurrence, is selected from 1 and 2;
- 10 r, at each occurrence, is selected from 0, 1, and 2;
- s, at each occurrence, is selected from 0, 1, and 2; and,
- t, at each occurrence, is selected from 0 and 1;
- 15 provided that A-B is other than benzyl-thiazolidin-2,4-dione.

[2] In a preferred embodiment, the present invention provides
 20 a novel compound of formula I, wherein;

- one of W, W¹, W², and W³ is C-D and the remaining are C-R¹;
- J is selected from N(Z-A-B) and CR(Z-A-B); and
- 25 J^a and J^b together are selected from CONHCR^{eR^f}, SO₂NHCR^{eR^f},
 (CR^{aR^b})_qSO₂NR^d, and (CR^{aR^b})_bCOCO(CR^{eR^f})_c, wherein b+c=0 or
 1;
- 30 alternatively, J and J^a together are selected from
 CON(Z-A-B)(CR^{cR^b}) and N(Z-A-B)Q(R^{cR^b})_a; and
- J^b is selected from NR^d, O, and CR^{eR^f};
- 35 Q is CO;

alternatively, J, J^a and J^b together are selected from
 CR(Z-A-B)(CR^{aR^b})_aQNR^d, CR(Z-A-B)(CR^{aR^b})_dC(O)O,

$\text{CR}(\text{Z-A-B})\text{NHCOCr}^{\text{eR}^{\text{f}}}$, $\text{CR}(\text{Z-A-B})\text{NHSO}_2\text{Cr}^{\text{eR}^{\text{f}}}$,
 $\text{N}(\text{Z-A-B})(\text{CR}^{\text{aR}^{\text{b}}})_{\text{a}}\text{QNR}^{\text{d}}$, $\text{N}(\text{Z-A-B})(\text{CR}^{\text{aR}^{\text{b}}})\text{C}(\text{O})\text{O}$,
 $\text{N}(\text{Z-A-B})\text{SO}_2(\text{CR}^{\text{cR}^{\text{b}}})_{\text{a}}\text{Cr}^{\text{eR}^{\text{f}}}$, $\text{N}(\text{Z-A-B})\text{SO}_2(\text{CR}^{\text{cR}^{\text{b}}})_{\text{a}}\text{NR}^{\text{d}}$,
 $\text{CON}(\text{Z-A-B})\text{Cr}^{\text{eR}^{\text{f}}}$, and $\text{CONR}^{\text{b}}(\text{CR}^{\text{cR}^{\text{b}}})_{\text{a}}\text{N}(\text{Z-A-B})$;

5

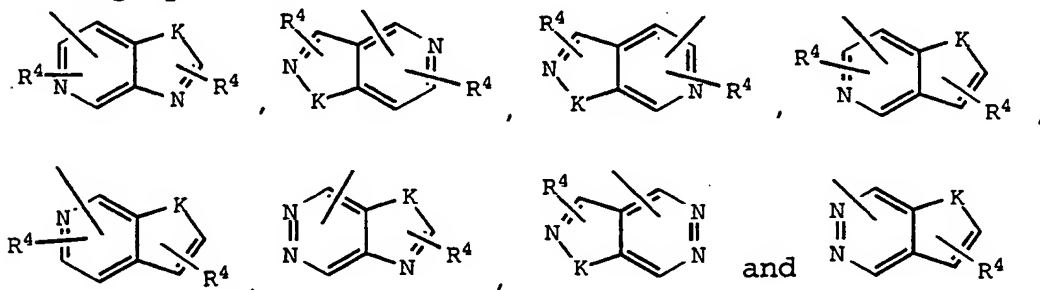
Z is selected from a CH_2O , OCH_2 , CH_2NH , NHCH_2 , $\text{CH}_2\text{C}(\text{O})$,
 $\text{C}(\text{O})\text{CH}_2$, $\text{C}(\text{O})\text{NH}$, $\text{C}(\text{O})\text{NH}$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$, SO_2NH , and
 SO_2NH ;

10 B is selected from: Y, X-Y, and $\text{NR}^2\text{R}^{2\text{a}}$;

Y is selected from one of the following carbocyclic and
 heterocyclic systems which are substituted with 0-2 $\text{R}^{4\text{a}}$;

phenyl, piperidinyl, piperazinyl, pyridyl,
 15 pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazole,
 thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-
 oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-
 20 thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-
 thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-
 triazole, 1,3,4-triazole, benzofuran, benzothiofuran,
 indole, benzimidazole, benzoxazole, benzthiazole,
 indazole, benzisoxazole, benzisothiazole, and
 25 isoindazole;

Y may also be selected from the following bicyclic heteroaryl
 ring systems:

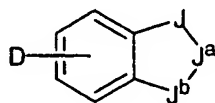


30

K is selected from O, S, NH, and N; and,

a, at each occurrence, is selected from 0 and 1.

[3] In an even more preferred embodiment, the present
5 invention provides a novel compound of formula Ia,



Ia

or stereoisomer or pharmaceutically acceptable salt thereof,
10 wherein;

D is $C(=NR^7)NR^8R^9$;

J is selected from $N(Z-A-B)$ and $CR(Z-A-B)$; and
15

J^a and J^b together are selected from $CONHCR^eR^f$;

alternatively, J and J^a together are selected from
20 $CON(Z-A-B)(CR^cR^b)$ and $N(Z-A-B)Q(R^cR^b)_a$; and

J^b is selected from NR^d , O, and CR^eR^f ;

Q is CO;

25 alternatively, J, J^a and J^b together are selected from
 $CR(Z-A-B)(CR^aR^b)_aQNR^d$, $CR(Z-A-B)(CR^aR^b)_aC(O)O$,
 $N(Z-A-B)(CR^aR^b)_aQNR^d$, $N(Z-A-B)(CR^aR^b)C(O)O$,
 $CON(Z-A-B)CR^eR^f$, and $CONR^b(CR^cR^b)_aN(Z-A-B)$;

30 A is selected from:

piperidinyl,

piperazinyl,

C_{5-6} carbocyclic residue substituted with 0-2 R^4 , and

5-6 membered heteroaryl containing from 1-4 heteroatoms
35 selected from the group consisting of N, O, and S and
substituted with 0-2 R^4 ; and,

B is selected from: Y and X-Y.

5 [4] In an even more preferred embodiment, the present invention provides a novel compound of formula Ia, wherein

J and J^a together are N(Z-A-B)C(O); and

10 J^b is selected from NR^d, O, and CR^eR^f;

alternatively, J, J^a and J^b together are CR(Z-A-B)C(O)NR^d;

Y is selected from one of the following carbocyclic and
15 heterocyclic systems which are substituted with 0-2 R^{4a};
phenyl, piperidinyl, piperazinyl, pyridyl,
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
isothiazolyl, pyrazolyl, imidazolyl, benzimidazole,
20 oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole,
1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole,
1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole,
1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-
triazole, and 1,3,4-triazole.

25

[5] In a still further preferred embodiment, the present invention provides a novel compound selected from:

30 1N-(2'-Aminosulfonyl-[1,1']biphenylamino)carbonylmethyl-6-amidinobenzimidazolinone;

1N-(2'-Aminosulfonyl-[1,1']biphenylamino)-carbonylmethyl-5-amidinobenzimidazolinone;

35

1N-[4'-(p-chlorophenyl)thiazolyl-2'-amino]carbonylmethyl-6-amidinobenzimidazolinone;

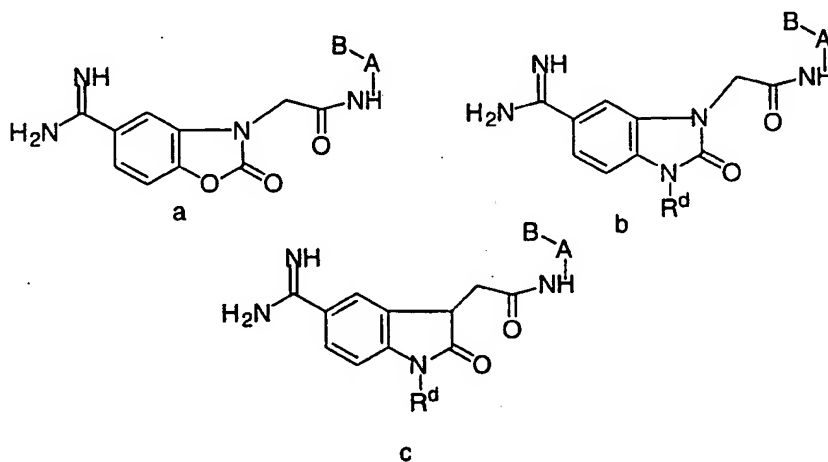
- 5-*Amidino-1N*-(1'-*N*-(4'-benzylpiperidino)carbonylmethyl)benzimidazolinone;
- 1*N*-(2'-Aminosulfonyl-[1,1']biphenylamino)carbonylmethyl-3*N*-β-hydroxyethylene-6-amidinobenzimidazolinone;
- 1*N*-(1'-*N*-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl)-6-amidinobenzoxazolinone;
- 1*N*-(*N*-*p*-(4'-oxazolyl)phenylamino)carbonylmethyl-6-amidino-benzoxazolinone;
- 1*N*-(1'-*N*-(4'-*N*-benzylsulfonylpiperazino)carbonylmethyl-6-amidino-benzoxazolinone;
- 7-amidino-1*N*-(4'-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1*H*)-one;
- 7-amidino-1*N*-(3'-amino-[1,1']biphenyl)carbonyl-methyl-3,4-dihydroquinoxalin-2(1*H*)-one;
- 7-amidino-1*N*-(4'-fluoro-[1,1']biphenyl)carbonyl-methyl-3,4-dihydroquinoxalin-2(1*H*)-one;
- 7-amidino-1*N*-[1,1']-biphenylcarbonylmethyl-3,4-dihydroquinoxalin-2(1*H*)-one;
- 7-amidino-1*N*-(2'-*tert*-butylsulfonamido-[1,1']biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1*H*)-one;
- 7-amidino-1*N*-(2'-sulfonamido-[1,1']-biphenyl)-carbonylmethyl-3,4-dihydroquinoxalin-2(1*H*)-one;
- 1*N*-(2'-aminosulfonyl-[1,1']biphenylamino)carbonyl-methyl-7-amidino-3,4-dihydroquinoxalin-2(1*H*)-one;

- 6-amidino-1N-[1,1']-biphenyl)carbonylmethyl-3,4-
dihydroquinoxalin-2(1H)-one;
- 1N-[1,1']Biphenylcarbonyl)ethyl-6-amidinobenzoxazolinone;
- 5 1-([1,1']-Biphenylcarbonyl)ethyl-6-amidino-3N-
methylbenzimidazolinone;
- 1-([1,1']-biphenylcarbonyl)ethyl-6-amidinobenzimidazolinone;
- 10 1N-(4-Bromophenylcarbonyl)ethyl-6-amidinobenzoxazolinone;
- 1N-[4-(2-Aminosulfonylphenyl)pyridin-2-yl]aminocarbonylmethyl-
6-amidinobenzoxazolinone;
- 15 1N-(4-Morpholinosulfonamidophenyl)aminocarbonylmethyl-6-
amidinobenzoxazolinone;
- 3-(3-methoxy-(2'-aminosulfonyl-[1,1']biphenyl-1-
aminocarbonyl)methyl-5-amidino-2-indolinone;
- 20 3-(3-amino-(2'-aminosulfonyl-[1,1']-
biphenylaminocarbonyl)methyl-5-amidino-2-indolinone;
- 25 3-(3-hydroxy-(2'-aminosulfonyl-[1,1']-
biphenylaminocarbonyl)methyl-5-amidino-2-indolinone;
- 3-(3'-hydroxy-(2-chloro-(2'-aminosulfonyl)-[1,1']-
biphenylaminocarbonyl)methyl-5-amidino-2-indolinone;
- 30 3-(3'-amino-(2-chloro-(2'-aminosulfonyl)-[1,1']-
biphenylaminocarbonyl)methyl-5-amidino-2-indolinone;
- 3-(2-chloro-(2'-aminosulfonyl)-[1,1']biphenyl-3'-
aminocarbonyl)methyl-5-amidino-2-indolinone;
- 35 3-(2-bromo-(2'-aminosulfonyl)-[1,1']biphenyl-3'-
aminocarbonyl)methyl-5-amidino-2-indolinone;

3-(2-fluoro-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl-5-amidino-2-indolinone; and,

5 3-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl-5-amidino-2-indolinone.

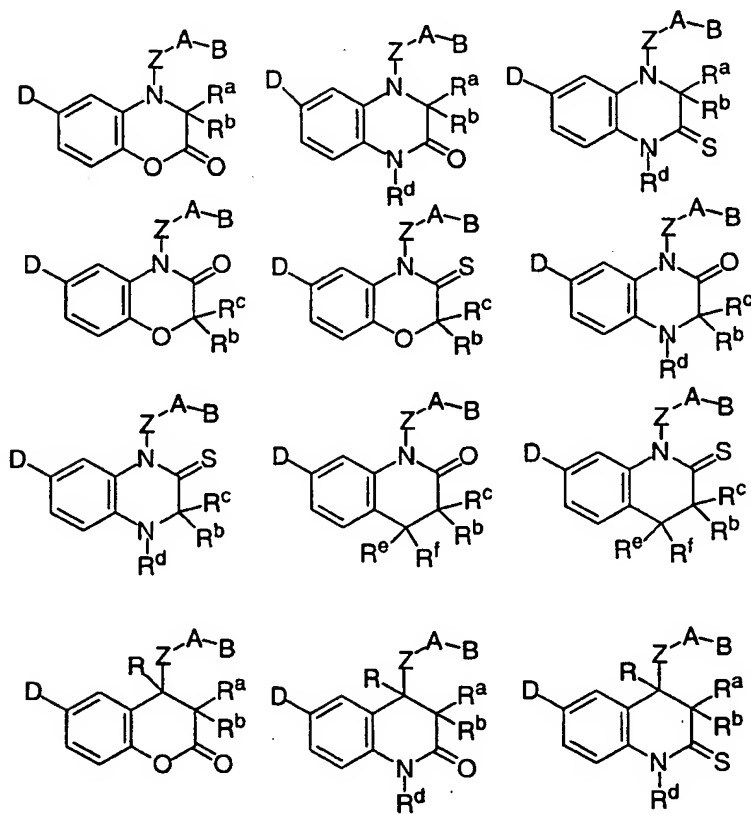
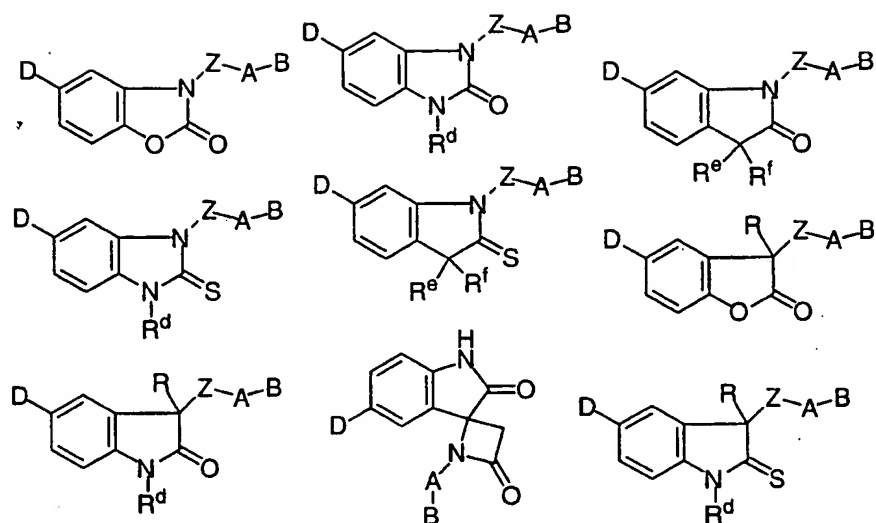
[6] In another preferred embodiment, the present invention
10 provides a compound of the formulae a-c:



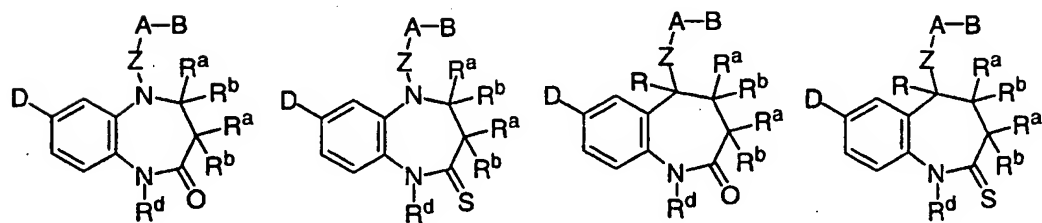
or stereoisomer or pharmaceutically acceptable salt form thereof.

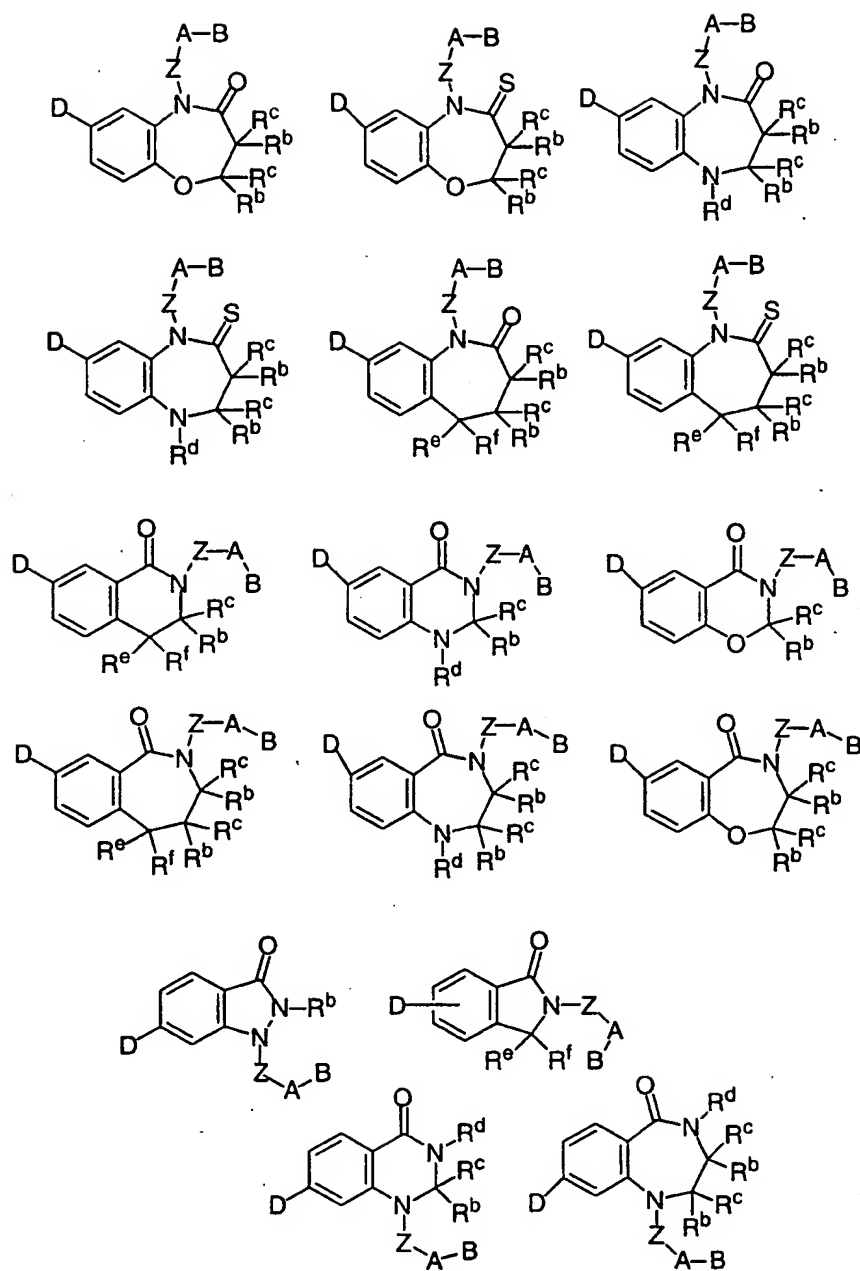
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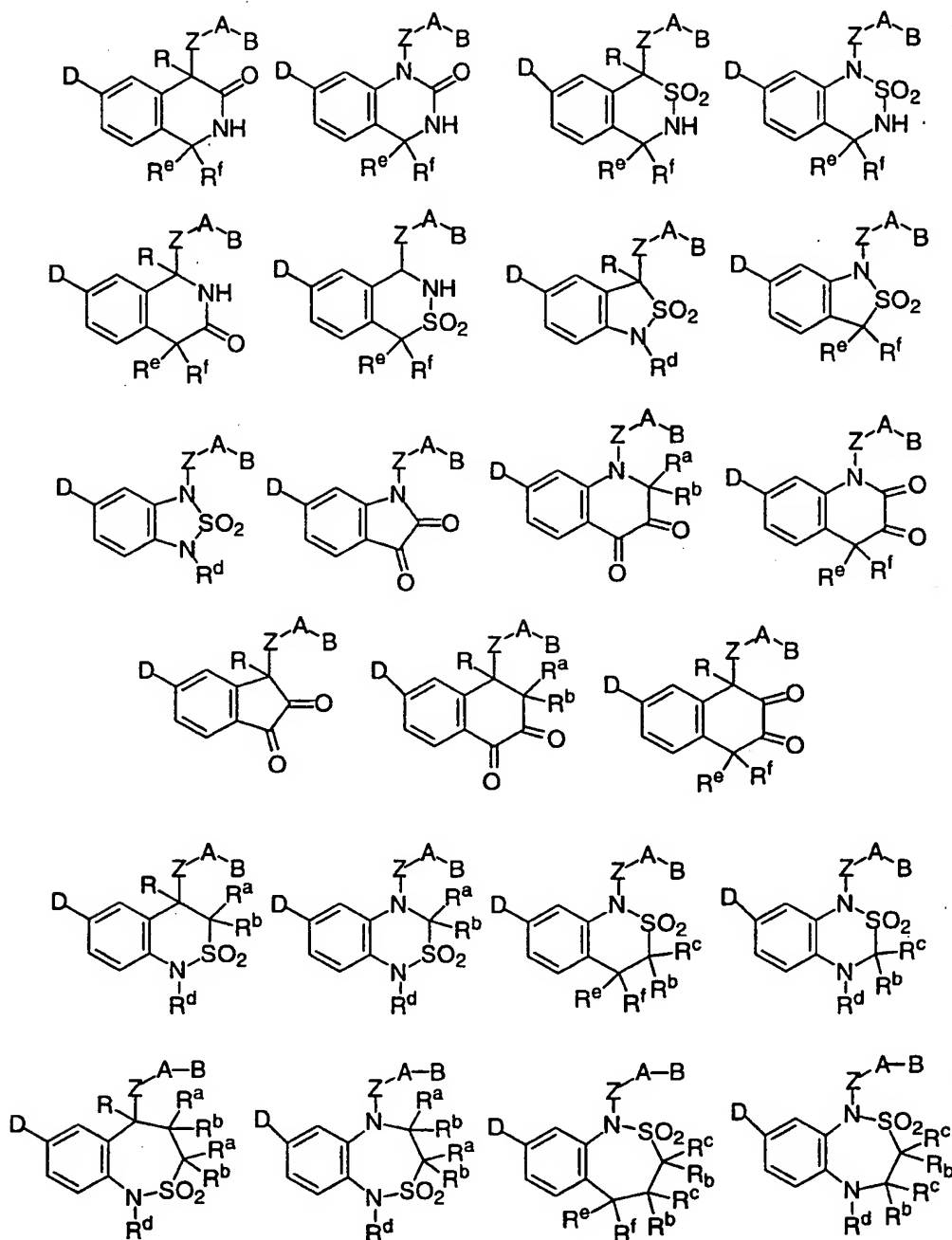
In a preferred embodiment, the present invention provides a compound of the formula:



5







5

In a third embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

10

In a fourth embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R⁶) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R⁶, then said group may optionally be substituted with up to two R⁶ groups and R⁶ at each occurrence is selected independently from the definition of R⁶. Also,

combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "C₁₋₆ alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl; "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,; [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic

heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyll, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, β -carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyll, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl,

isoxazolyl, morpholinyl, naphthyridinyl,
octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-
oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
oxazolidinyl., oxazolyl, oxazolidinylperimidinyl,
5 phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl,
phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl,
piperazinyl, piperidinyl, pteridinyl, piperidonyl,
4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl,
pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl,
10 pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl,
pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl,
quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl,
quinuclidinyl, carbolinyl, tetrahydrofuranly,
tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-
15 thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-
thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl,
thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl,
thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred
20 heterocycles include, but are not limited to, pyridinyl,
furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl,
benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl,
benzisoxazolyl, oxindolyl, benzoxazoliny, or isatinoyl. Also
included are fused ring and spiro compounds containing, for
25 example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed
herein to refer to those compounds, materials, compositions,
and/or dosage forms which are, within the scope of sound
medical judgment, suitable for use in contact with the tissues
30 of human beings and animals without excessive toxicity,
irritation, allergic response, or other problem or
complication, commensurate with a reasonable benefit/risk
ratio.

As used herein, "pharmaceutically acceptable salts" refer
35 to derivatives of the disclosed compounds wherein the parent
compound is modified by making acid or base salts thereof.
Examples of pharmaceutically acceptable salts include, but are
not limited to, mineral or organic acid salts of basic

residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is

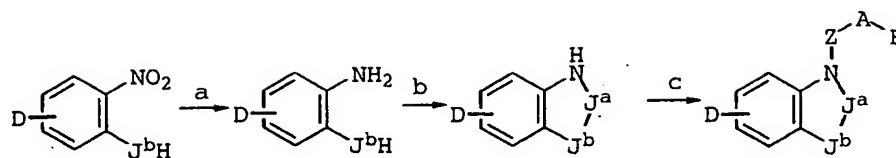
administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like. Preferred prodrugs are amine prodrugs the amine group is attached to a group selected from OH, C₁₋₄ alkoxy, C₆₋₁₀ aryloxy, C₁₋₄ alkoxy carbonyl, C₆₋₁₀ aryloxy carbonyl, C₆₋₁₀ arylmethyl carbonyl, C₁₋₄ alkyl carbonyloxy C₁₋₄ alkoxy carbonyl, and C₆₋₁₀ aryl carbonyloxy C₁₋₄ alkoxy carbonyl. More preferred prodrugs are OH, methoxy, ethoxy, benzyloxy carbonyl, methoxy carbonyl, and methyl carbonyloxymethoxy carbonyl.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

The compounds of Formula I can be prepared using the reactions and techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991).

Scheme 1

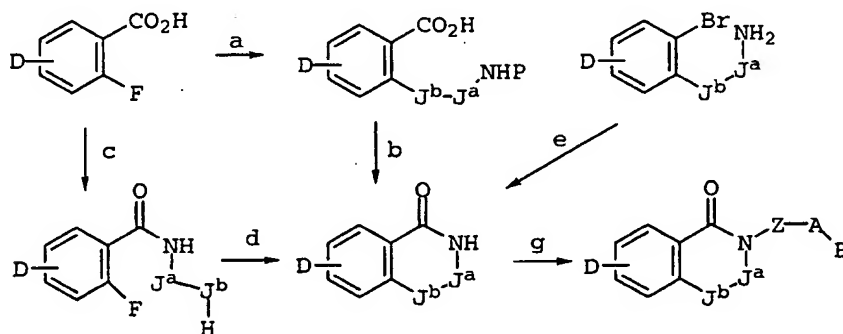


- 5 The generic cores depicted in Scheme 1 can be made from nitro compounds or from the replacement of the corresponding halogen with the HNR^{d} - or HO-fragments in the presence of a base. Reduction of the nitro group can provide anilines. Cyclization of the anilines with formic acid,
- 10 trialkylorthoformate, phosgene, carbon disulfide, sulfuryl chloride, oxalyl chloride, α -chloroacetyl chloride, β -chloroacetyl chloride, α -chloroacetal, β -chloroacetate, α -chlorosulfonyl chloride, or β -chlorosulfonyl chloride can form the cyclic cores. Alkylation of the NH on the new formed ring
- 15 with halo-ZAB can provide the desired compound.

The thioamides and thioesters of the present invention can be obtained from the corresponding amides and esters by treatment with P_2S_5 in the presence of a base, or with Lawesson's reagent (T. Nishio et al, *Synthesis* **1989**, 5, 396).

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Scheme 2

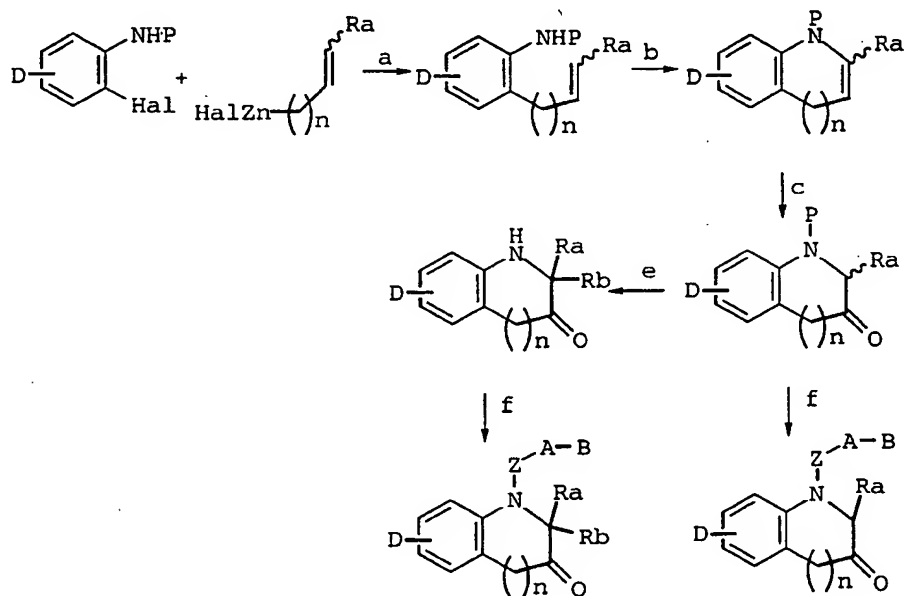


- 25 The 6,6-fused compounds described in Scheme 2 can be prepared starting with nucleophilic substitution of the aryl fluoride with HJaJbNHP in the presence of a base. After removal of the protecting group P, intramolecular cyclization with a dehydration reagent can give the desired cores.

Alternatively, dehydration of the acid with $HJ^aJ^bNH_2$, followed by intramolecular nucleophilic substitution of the aryl fluoride by the J^bH -fragment in the presence of a base, can give the desired cores. Furthermore, ω -(2-bromo-

- 5 phenyl)alkylamines can react with carbon monoxide in the presence of palladium catalyst to give the desired cores.

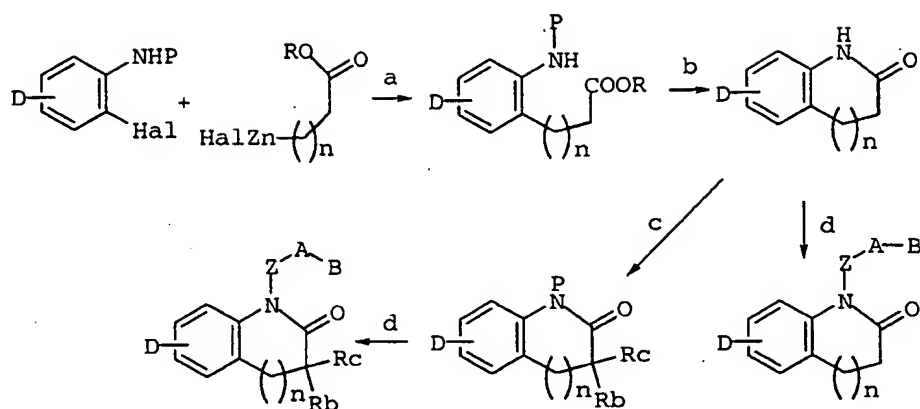
Scheme 3



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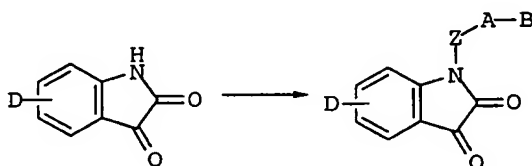
- The generic cores depicted in Scheme 3 can be prepared from *N*-protected *o*-halo-anilines. The anilines can also be made from the non-protected anilines or the nitro precursors.
- 15 Palladium catalyzed coupling reaction of the halides with zinc reagents containing vinyl functionality can give the coupled compounds. In the presence of palladium catalyst, intramolecular cyclizations can produce ring closed compounds, which can be oxidized with MCPBA to give the 3-oxo cores. The
- 20 3-oxo derivatives can be further elaborated, followed by the *N*-alkylation with halo-ZAB, to provide the desired compounds.

Scheme 4



- 5 The N-substituted cores illustrated in Scheme 4 can be obtained from N-protected o-halogen anilines. Metal catalyzed coupling of the halide with a zinc reagent which contains an ester functionality can give the coupled compound. Deprotection of the P-group from the nitrogen can give the
- 10 cyclic compound. Further elaboration and N-alkylation can be performed as described previously.

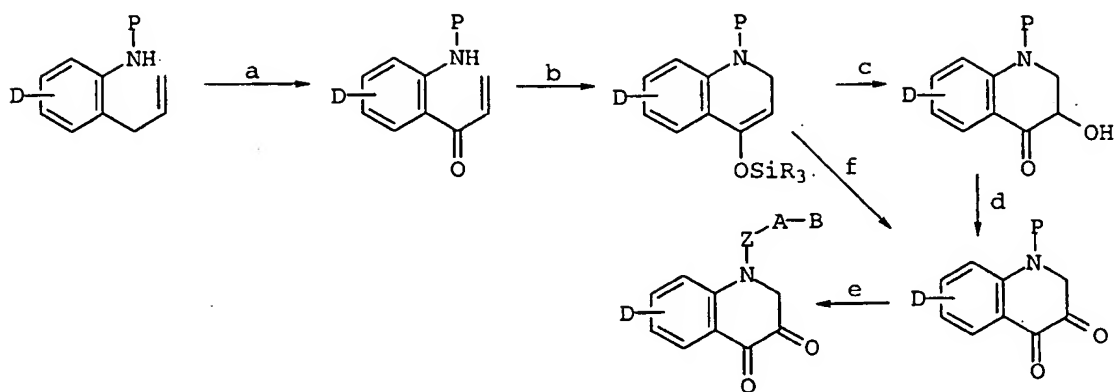
Scheme 5



15

- Bromine on commercially available 5-bromoisatin can be converted to other functionalities by palladium catalyzed cross coupling reactions and nucleophilic replacements. The
- 20 desired compounds can then be obtained by N-alkylation with halo-ZAB.

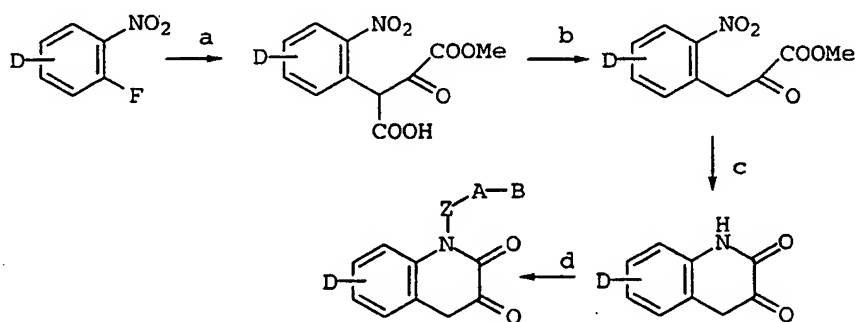
Scheme 6



5 Scheme 6 provides a route to some of the diketones of the present invention. Oxidation of o-allylaniline (see Scheme 3) with MnO₂ can provide a ketone. The ketone can then undergo Michael addition, followed by quenching with chlorosilane, to give the cyclic vinyl silylether. The vinyl silylether can be
 10 oxidized with NMMO in the presence of OsO₄ to form the α-hydroxyketone, which can be further oxidized with Pb(OAc)₄ in pyridine to form the diketone. The desired compound can be obtained by N-alkylation with an appropriate halo-ZAB.

15

Scheme 7

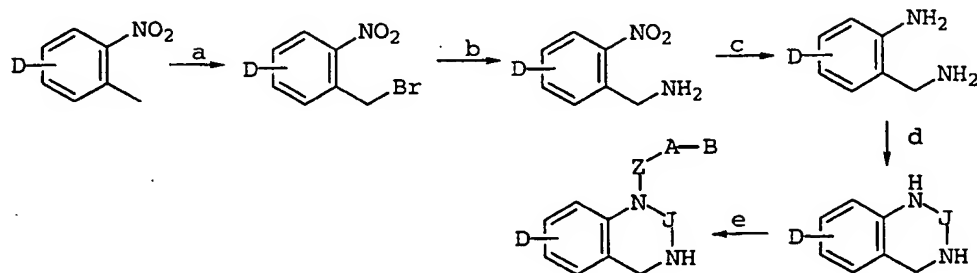


Preparation of additional diketones is shown in Scheme 7.
 20 Nucleophilic substitution of the aryl fluoride with 2-ketosuccinic acid monomethyl ester, followed by decarboxylation, can give β-aryl-α-ketoester. Protection of the carbonyl group, reduction of the nitro group, and

deprotection of the carbonyl group can afford the final intermediate which is then cyclized and alkylated.

Scheme 8

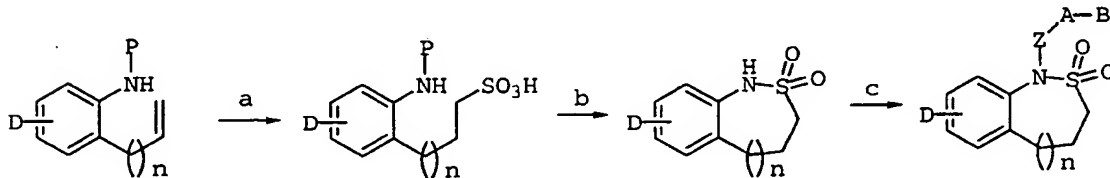
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6,6-Fused ureas/sulfonylureas can be made as shown in Scheme 8 ($J = \text{CO}, \text{SO}_2$). Bromination of 2-methyl nitrobenzene with NBS can give the benzyl bromide, which can be readily converted into the amine. After reduction of the nitro group, cyclization with COCl_2 or SO_2Cl_2 can afford the desired cores.

Scheme 9

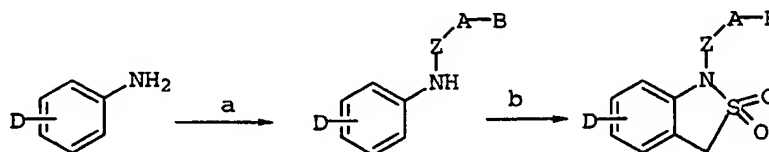
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Scheme 9 illustrates a route to fused sulfonamides. Addition of NaHSO_3 to the olefin (see Scheme 3) can give the corresponding sulfuric acid (Li, C. *Synthesis* **1991**, 244). Removal of the P-group and then dehydration with the sulfuric acid can provide sulfonamide, which can undergo N-alkylation to afford the desired products.

25

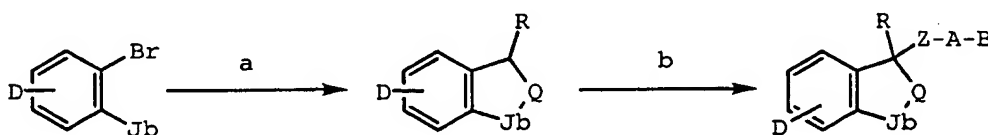
Scheme 10



In Scheme 10 is shown a route to a 6,5-fused sulfonamide. N-alkylation of the aniline with halo-ZAB, followed by treatment with $\text{ClCH}_2\text{SO}_2\text{Cl}$ and a base, can give the desired

5 core (Wojciechowski, K. *Synthesis* **1992**, 571).

Scheme 11

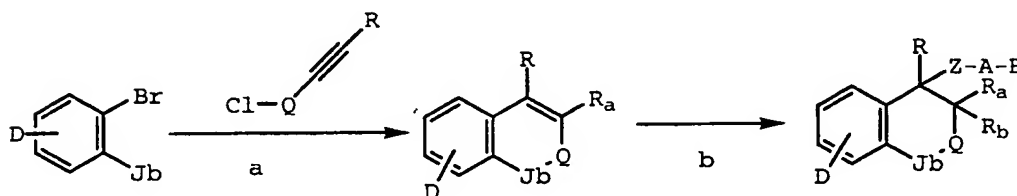


10

The 6,5-fused heterocyclic rings wherein J^b is N-R^d or O are prepared by rhodium coupling with an appropriate azide, Cl-Q-CH(R)N_2 (Scheme 11). Deprotonation of the benzylic methine with LDA at followed by addition of the corresponding

15 halo-ZAB affords the desired product.

Scheme 12



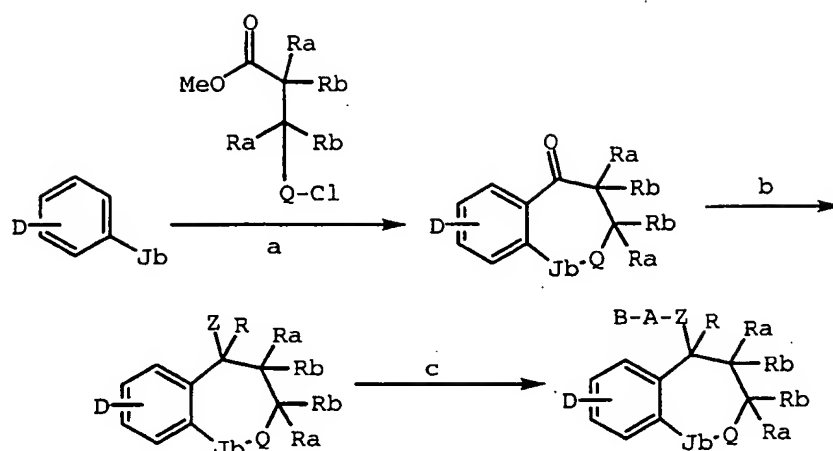
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Synthesis of the 6,6-fused heterocycles (J^b is N-R^d or O) may be obtained via radical addition to an acetylene derivative as shown (e.g., Bu_3SnH) or transmetallation of the aromatic bromine with $n\text{-BuLi}$ or palladium coupling with

25 Pd(OAc)_2 and finally quenching with the desired R^a -halo compound to afford the intermediate shown in Scheme 12. Cuprate addition (Li(CN)Cu-Z-A-B) and quenching again with the appropriate R^b -halo compound should afford the desired 6,6-fused heterocycle target.

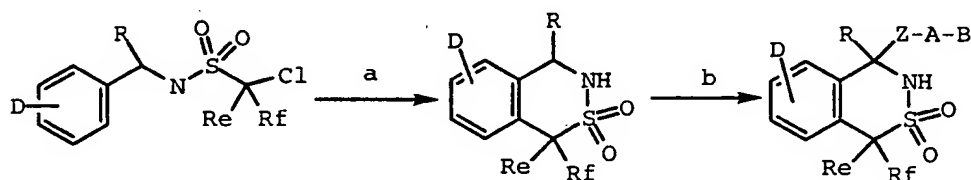
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Scheme 13



- 5 Acylation of an anilino or phenolic starting reagent (J^b
 = N-R^d or O) with a functionalized methyl ester acid chloride
 followed by saponification should afford the desired acid
 intermediate (Scheme 13). Chlorination to the acid chloride
 10 intermediate which can then subjected to the Friedel Crafts
 conditions to afford the target heterocycle. The resulting
 heterocycle may be further functionalized via a Wittig
 olifination, followed by hydrogenation and alkylation to yield
 the fully functionalized heterocycle. The benzylic Z-group
 15 can then coupled to the A-B groups to afford the target
 compound.

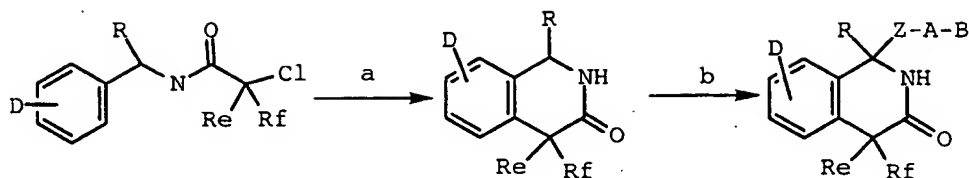
Scheme 14



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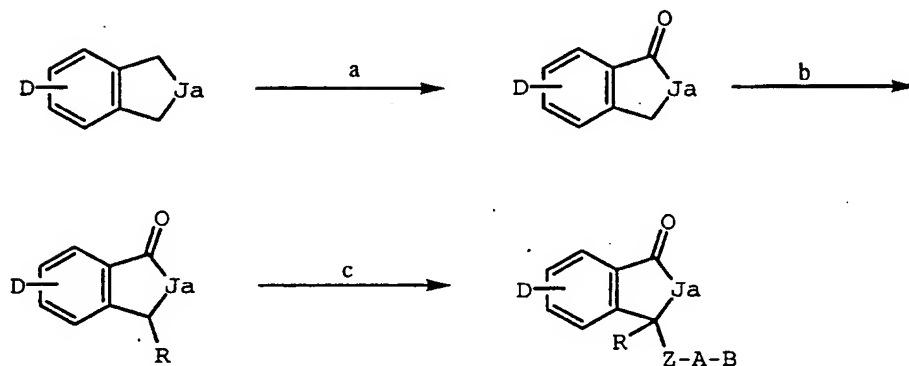
- The 6,6 sulfonamides in Scheme 14 may be prepared from
 the appropriate halo sulfonamide using NaOH and DMSO
 (Synthesis 1992, (6), 571-6). Alkylation with NaH and halo-
 25 ZAB should afford the desired target. This same method may be
 used to prepared the 6,6-fused cyclic amides in Scheme 15.

Scheme 15



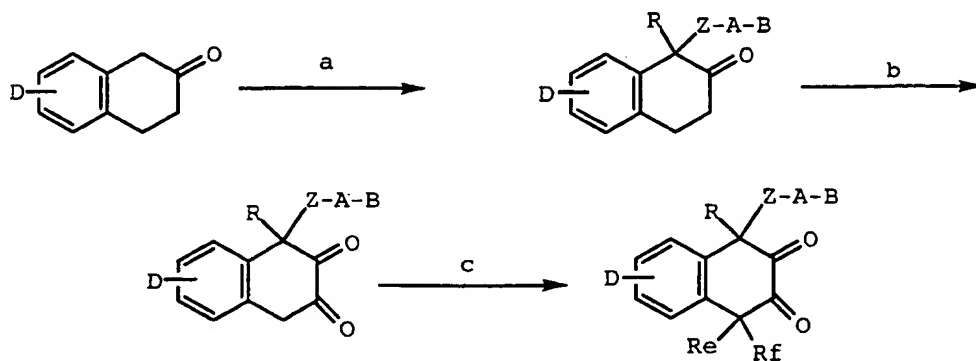
5

Scheme 16



10 5,6-Fused isatins can be prepared from the corresponding
indanone (Scheme 16). Oxidation with SeO_2 in acetic acid
followed by alkylation or bromination/hydrolysis should afford
the key isatin intermediate (*J. Chem. Soc., Perkin Trans.*
1995, 1(24), 3117-24). This may then be alkylated with the
15 corresponding halo-ZAB to afford the desired isatin target.

Scheme 17



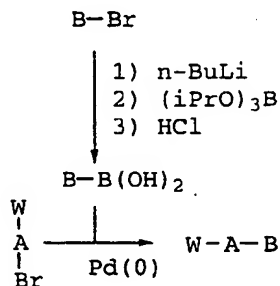
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The 6,6-fused carbocycles shown in Scheme 17 may be prepared from the corresponding 3-tetralone via alkylation with NaH R-halo or NBS, followed by a second alkylation with halo-ZAB. Oxidation with SeO₂ affords the desired diketone which is then dialkylated with R^e-halo and R^f-halo sequentially using NaH as the base to yield the desired target.

Preparation of group A-B of FORMULA I

Compounds of this invention where B is either a carbocyclic or heterocyclic residue as defined in Formula I are coupled to A as shown generically and by specific example in Schemes 18 and 19, respectively. Either or both of A and B may be substituted with 0-2 R⁴. W is defined as a suitable protected nitrogen, such as NO₂ or NHBOC; a protected sulfur, such as S-tBu or SMOM; or a methyl ester. Halogen-metal exchange of the bromine in bromo-B with n-butyl lithium, quenching with triisopropyl borate and acidic hydrolysis gives the required boronic acid, B-B(OH)₂. The W-A-Br subunit may be already linked to ring M before the Suzuki coupling reaction. Deprotection provides the complete subunit.

Scheme 18

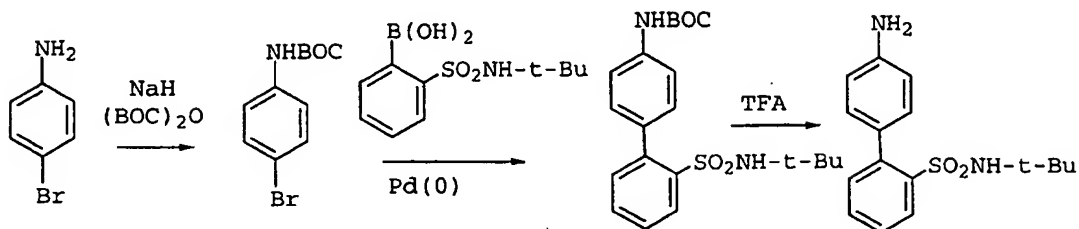


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Scheme 19 describes a typical example of how the A-B subunit is prepared for attachment to ring M. 4-Bromoaniline is protected as Boc-derivative and the coupled to 2-(t-butylamino)sulfonylphenylboronic acid under Suzuki conditions. 2-(t-Butylamino)sulfonylphenylboronic acid is prepared by the method described by Rivero (*Bioorg. Med. Chem. Lett.* **1994**, 189). Deprotection with TFA can provide the aminobiphenyl

compound. The aminobiphenyl is then coupled to the core ring structures as described below.

Scheme 19



When B is defined as X-Y, the following description applies. Groups A and B are available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of organic synthesis. the required reactive functional groups appended to analogs of A and B are also available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of synthesis. In the tables that follow the chemistry required to effect the coupling of A to B is outlined.

Table A: Preparation of Amide Ester, Urea, Sulfonamide and Sulfamide Linkages Between A and B.

If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-NHR ² as a substituent	ClC(O)-Y	A-NR ² -C(O)-Y
a secondary NH as part of a ring or chain	ClC(O)-Y	A-C(O)-Y
A-OH as a substituent	ClC(O)-Y	A-O-C(O)-Y
A-NHR ² as a substituent	ClC(O)-CR ² R ^{2a} -Y	A-NR ² -C(O)-CR ² R ^{2a} -Y

a secondary NH as part of a ring or chain	$\text{ClC(O)-CR}^2\text{R}^{2a}\text{-Y}$	$\text{A-C(O)-CR}^2\text{R}^{2a}\text{-Y}$
A-OH as a substituent	$\text{ClC(O)-CR}^2\text{R}^{2a}\text{-Y}$	$\text{A-O-C(O)-CR}^2\text{R}^{2a}\text{-Y}$
A-NHR^2 as a substituent	$\text{ClC(O)-CNR}^2\text{-Y}$	$\text{A-NR}^2\text{-C(O)-CNR}^2\text{-Y}$
a secondary NH as part of a ring or chain	$\text{ClC(O)-CNR}^2\text{-Y}$	$\text{A-C(O)-CNR}^2\text{-Y}$
A-OH as a substituent	$\text{ClC(O)-CNR}^2\text{-Y}$	$\text{A-O-C(O)-CNR}^2\text{-Y}$
A-NHR^2 as a substituent	$\text{ClSO}_2\text{-Y}$	$\text{A-NR}^2\text{-SO}_2\text{-Y}$
a secondary NH as part of a ring or chain	$\text{ClSO}_2\text{-Y}$	$\text{A-SO}_2\text{-Y}$
A-NHR^2 as a substituent	$\text{ClSO}_2\text{-CR}^2\text{R}^{2a}\text{-Y}$	$\text{A-NR}^2\text{-SO}_2\text{-CR}^2\text{R}^{2a}\text{-Y}$
a secondary NH as part of a ring or chain	$\text{ClSO}_2\text{-CR}^2\text{R}^{2a}\text{-Y}$	$\text{A-SO}_2\text{-CR}^2\text{R}^{2a}\text{-Y}$
A-NHR^2 as a substituent	$\text{ClSO}_2\text{-NR}^2\text{-Y}$	$\text{A-NR}^2\text{-SO}_2\text{-NR}^2\text{-Y}$
a secondary NH as part of a ring or chain	$\text{ClSO}_2\text{-NR}^2\text{-Y}$	$\text{A-SO}_2\text{-NR}^2\text{-Y}$
A-C(O)Cl	HO-Y as a substituent	A-C(O)-O-Y
A-C(O)Cl	$\text{NHR}^2\text{-Y}$ as a substituent	$\text{A-C(O)-NR}^2\text{-Y}$
A-C(O)Cl	a secondary NH as part of a ring or chain	A-C(O)-Y
$\text{A-CR}^2\text{R}^{2a}\text{C(O)Cl}$	HO-Y as a substituent	$\text{A-CR}^2\text{R}^{2a}\text{C(O)-O-Y}$
$\text{A-CR}^2\text{R}^{2a}\text{C(O)Cl}$	$\text{NHR}^2\text{-Y}$ as a substituent	$\text{A-CR}^2\text{R}^{2a}\text{C(O)-NR}^2\text{-Y}$

$A-CR^2R^{2a}C(O)Cl$	a secondary NH as part of a ring or chain	$A-CR^2R^{2a}C(O)-Y$
$A-SO_2Cl$	NHR^2-Y as a substituent	$A-SO_2-NR^2-Y$
$A-SO_2Cl$	a secondary NH as part of a ring or chain	$A-SO_2-Y$
$A-CR^2R^{2a}SO_2Cl$	NHR^2-Y as a substituent	$A-CR^2R^{2a}SO_2-NR^2-Y$
$A-CR^2R^{2a}SO_2Cl$	a secondary NH as part of a ring or chain	$A-CR^2R^{2a}SO_2-Y$

The chemistry of Table A can be carried out in aprotic solvents such as a chlorocarbon, pyridine, benzene or toluene, at temperatures ranging from $-20^{\circ}C$ to the reflux point of the solvent and with or without a trialkylamine base.

Table B: Preparation of Ketone Linkages between A and B.

If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
$A-C(O)Cl$	$BrMg-Y$	$A-C(O)-Y$
$A-CR^2R^{2a}C(O)Cl$	$BrMg-Y$	$A-CR^2R^{2a}C(O)-Y$
$A-C(O)Cl$	$BrMgCR^2R^{2a}-Y$	$A-C(O)CR^2R^{2a}-Y$
$A-CR^2R^{2a}C(O)Cl$	$BrMgCR^2R^{2a}-Y$	$A-CR^2R^{2a}C(O)CR^2R^{2a}-Y$

The coupling chemistry of table B can be carried out by a variety of methods. The Grignard reagent required for Y is prepared from a halogen analog of Y in dry ether, dimethoxyethane or tetrahydrofuran at $0^{\circ}C$ to the reflux point of the solvent. This Grignard reagent can be reacted directly under very controlled conditions, that is low temperature ($-20^{\circ}C$ or lower) and with a large excess of acid chloride or with catalytic or stoichiometric copper bromide-dimethyl sulfide complex in dimethyl sulfide as a solvent or with a variant thereof. Other methods available include transforming

the Grignard reagent to the cadmium reagent and coupling according to the procedure of Carson and Prout (Org. Syn. Col. Vol. 3 601, 1955) or coupling mediated by $\text{Fe}(\text{acac})_3$ according to Fiandanesse et al. (Tet. Lett., 4805, 1984), or a coupling mediated by manganese(II) catalysis (Cahiez and Laboue, Tet. Lett., 33(31), 4437, 1992).

Table C: Preparation of Ether and Thioether linkages between A and B.

If A contains:	then the reactive substituent of Y is:	to give the following product A-X-Y:
A-OH	Br-Y	A-O-Y
A-CR ² R ^{2a} -OH	Br-Y	A-CR ² R ^{2a} O-Y
A-OH	Br-CR ² R ^{2a} -Y	A-OCR ² R ^{2a} -Y
A-SH	Br-Y	A-S-Y
A-CR ² R ^{2a} -SH	Br-Y	A-CR ² R ^{2a} S-Y
A-SH	Br-CR ² R ^{2a} -Y	A-SCR ² R ^{2a} -Y

10

The ether and thioether linkages of Table C can be prepared by reacting the two components in a polar aprotic solvent such as acetone, dimethylformamide or dimethylsulfoxide in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide at a temperature ranging from ambient to the reflux point of the solvent used.

15

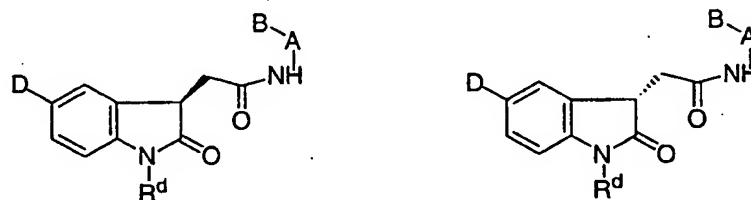
Table D: Preparation of -SO- and -SO₂- linkages from thioether of Table C.

20

If the starting material is:	then it is oxidized with wet Alumina/Oxone to give:	then it is oxidized with m-chloroperbenzoic acid to give:
A-S-Y	A-S(O)-Y	A-SO ₂ -Y
A-CR ² R ^{2a} S-Y	A-CR ² R ^{2a} S(O)-Y	A-CR ² R ^{2a} SO ₂ -Y
A-SCR ² R ^{2a} -Y	A-S(O)CR ² R ^{2a} -Y	A-SO ₂ CR ² R ^{2a} -Y

The thioethers of Table C serve as a convenient starting material for the preparation of the sulfoxide and sulfone analogs of Table D. A combination of wet alumina and Oxone can provide a reliable reagents for the oxidation of the thioether to the sulfoxide as shown by Greenhalgh (*Syn. Lett.* **1992**, 235). The sulfone can be prepared according to the method of Satoh (*Chem. Lett.* **1992**, 381) using m-chloroperbenzoic acid.

A compound of Formula I may have more than one isomer and one of the isomers may display superior activity compared with the other. Thus, each isomer is contemplated to be a part of the present invention. For example, both stereoisomers of the following indolinones are considered to be part of the present invention.



When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy*, **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g. Andrew S. Thompson, et al, *Tet. lett.* **1995**, 36, 8937-8940. In addition, separation may be achieved by selective crystallization, optionally in the presence of a chiral acid or base thereby forming a chiral salt.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration to the invention and are not intended to be limiting thereof.

EXAMPLES

Examples 1 and 2

1N-(2'-Aminosulfonyl-[1,1']biphenylamino)carbonylmethyl-6-amidinobenzimidazolinone (Example 1) and 1N-(2'-Aminosulfonyl-[1,1']biphenylamino)-carbonylmethyl-5-amidinobenzimidazolinone (Example 2)

Preparation of 6-Cyanobenzimidazolinone.

After 4-amino-3-nitrobenzonitrile (3.26 g, 20 mmol) was treated with hydrogen in MeOH (300 mL) in the presence of 5% palladium on active carbon (1 g) at room temperature for 16 hours, the reaction mixture was filtered and the filtrate was concentrated to give 3,4-diaminobenzonitrile (2.4 g, 90% yield). A solution of 3,4-diaminobenzonitrile (2 g, 15 mmol) in THF (100 mL) was treated with carbonyldiimidazole (CDI, 3.2 g, 19 mmol) at room temperature for 18 hours. The mixture was diluted with EtOAc (150 mL), washed with 1N HCl (30 mL) and brine, and dried over MgSO₄. Filtration and concentration gave 5-cyanobenzimidazolinone (1.9 g, 80%). ¹H NMR (CD₃OD) δ 7.40 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H); MS: 160.1 (M+H)⁺.

Preparation of 2'-tert-butylaminosulfonyl-[1,1']biphenylaminocarbonylmethylene chloride.

Acylation of 4-[(o-SO₂NHtBu)-phenyl]aniline (3 mmol) with 2-chloroacetyl chloride (4 mmol) in CH₃CN (100 mL) in the presence of K₂CO₃ (4 mmol) was carried out at rt for 16 hours. The mixture was filtered. The filtrate was extracted with EtOAc, washed with water, dried over MgSO₄, and concentrated to give the product in almost quantitative yield. ¹H NMR (CD₃OD) δ 8.34 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.59-7.46 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 4.23 (s, 2H), 3.58 (s, 1H), 1.02 (s, 9H); MS(CI): m/z 381 (M+H)⁺.

Preparation of 1N-(2'-tert-butylaminosulfonyl-[1,1']biphenylamino)carbonylmethyl-6-cyanobenzimidazolinone and 1N-(2'-tert-butylaminosulfonyl-[1,1']biphenylamino)carbonylmethyl-5-cyano-benzimidazolinone.

5

A solution of 5-cyanobenzimidazolinone (159 mg, 1 mmol) in DMF (5 mL) was treated with NaH (4 mmol), followed by addition of 1N-(2'-tert-butylaminosulfonyl-[1,1']-biphenylamino)carbonylmethyl chloride (380 mg, 1 mmol). The resulting mixture was stirred at room temperature for 18 hours, and then was extracted with EtOAc. The organic layer was washed with water and brine, and dried over MgSO₄, followed by purification and isolation on HPLC, to give 1N-(2'-tert-butylaminosulfonyl-[1,1']-biphenylamino)-carbonylmethyl-6-cyanobenzimidazolinone (80 mg, 16%) and 1N-(2'-tert-butylaminosulfonyl-[1,1']-biphenylamino)-carbonylmethyl-5-cyanobenzimidazolinone (120 mg, 24%). Both regioisomers have ESMS m/z: 465 (M+H). For the 6-cyano isomer: ¹H NMR (CD₃OD) δ 8.11 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.63-7.62 (m, 1H), 7.51 (td, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.47 (dd, J = 8.4 Hz, J = 1.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.43-7.42 (m, 1H), 7.32 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 4.82 (s, 2H), 0.99 (s, 9H); ¹³C NMR (CD₃OD) δ 167.28, 156.85, 143.46, 141.60, 139.10, 137.26, 135.85, 133.90, 133.05, 131.49, 130.16, 129.53, 128.75, 127.52, 120.59, 120.42, 113.58, 110.14, 105.64, 54.99, 44.56, 30.06. For the 5-cyano isomer: ¹H NMR (CD₃OD) δ 8.08 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.63-7.56 (m, 3H), 7.49 (td, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.43-7.42 (m, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.30 (dd, J = 7.6 Hz, J = 7.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 2.01 (s, 2H), 0.99 (s, 9H).

Preparation of 1N-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl-6-amidinobenzimidazolinone and 1N-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl-5-amidinobenzimidazolinone.

A solution of 1*N*-(2'-*tert*-butylaminosulfonyl-[1,1']-biphenylamino)carbonylmethyl-6-cyanobenzimidazolinone (0.16 mmol) in EtOH (10 mL) was saturated with HCl gas and stirred at 0°C for 16 hours. The solution was concentrated to give a residue, which was treated with NH₄OAc (42 mg, 0.64 mmol) in 2*N* NH₃ in EtOH (10 mL) at rt for 16 hours. After the mixture was concentrated, the residue was purified by HPLC to give the title compound (45 mg, 61%). By using general Pinner reaction conditions, 1*N*-(2'-*tert*-butylaminosulfonyl-[1,1']-biphenylamino)carbonylmethyl-5-cyanobenzimidazolinone (0.24 mmol) was converted to its amidino derivative (60 mg, 54%).

For Example 1: ¹H NMR (CD₃OD) δ 8.08 (dd, *J* = 8.5 Hz, *J* = 1.5 Hz, 1H), 7.62 (dt, *J* = 8.5 Hz, *J* = 1.5 Hz, 2H), 7.59-7.55 (m, 3H), 7.50 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.39 (dt, *J* = 8.4 Hz, *J* = 1.5 Hz, 2H), 7.31 (dd, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 4.82 (s, 2H); ¹³C NMR (CD₃OD) δ 168.44, 167.52, 156.97, 143.08, 141.54, 139.03, 137.37, 134.89, 133.66, 132.92, 132.70, 131.26, 128.73, 128.61, 123.56, 122.07, 120.58, 110.74, 108.96, 44.63; ESMS: 465 (M+H)⁺; HRMS: (M+H) calcd. for C₂₂H₂₀N₆O₄S₁ 465.1345, found 465.1335; Anal.: (C₂₂H₁₈N₄O₁+1.5TFA+ 0.08HCl+1H₂O) C, H, N, S, F, Cl. For Example 2: ¹H NMR (CD₃OD): δ 8.09 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.59-7.54 (m, 2H), 7.54-7.50 (m, 2H), 7.40 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.86 (s, 2H); ESMS: 465.4 (M+H)⁺.

Example 3

1*N*-[4'-(*p*-chlorophenyl)thiazolyl-2'-amino]carbonylmethyl-6-amidinobenzimidazolinone

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Preparation of 1*N*-[4'-(*p*-chlorophenyl)thiazolyl-2'-amino]carbonylmethyl-6-amidinobenzimidazolinone.

A mixture of 1*N*-Boc-5-cyano-benzoimidazolinone (210 mg, 0.81 mmol), 2-(2-chloroacetamido)-4-(*p*-chlorophenyl)-5-thiazole (255 mg, 0.89 mmol), and K₂CO₃ (138 mg, 1.0 mmol) in acetone (10 mL) was stirred at 68°C for 18 hours. The mixture was diluted with EtOAc (150 mL), washed with water and brine,

and dried over MgSO_4 . Concentration gave a crude product, which underwent a Pinner reaction, followed by HPLC purification, to give the product (150 mg, 43.3% for the two steps). ^1H NMR (CD_3OD) δ 7.88 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.1 Hz, 1H), 4.93 (s, 2H); ^{13}C NMR (CD_3OD) δ 168.51, 167.09, 159.04, 156.88, 150.20, 136.79, 134.66, 134.55, 130.31, 129.76, 128.53, 123.70, 123.17, 122.65, 109.89, 109.49, 109.81, 44.01; ESMS: m/z 427.2 (M+H) $^+$; HRMS: (M+H) calcd. for $\text{C}_{19}\text{H}_{15}\text{N}_6\text{O}_2\text{S}_1\text{Cl}_1$ 427.0744, found 427.0743; Anal.: ($\text{C}_{19}\text{H}_{15}\text{N}_6\text{O}_2\text{S}_1\text{Cl}_1 + 1.57\text{TFA} + 0.22\text{HCl} + 3\text{H}_2\text{O}$) C, H, N, S, F, Cl.

Example 4

5-Amidino-1*N*-(1'*N*-(4'-benzylpiperidino)carbonylmethyl)benzimidazolinone

Preparation of 1*N*-(4-benzylpiperidino)carbonylmethylchloride.

A solution of 4-benzylpiperidine (17.5 g, 100 mmol) in THF (250 mL) was treated with K_2CO_3 (14 g, 101 mmol) and chloroacetylchloride (11.3 g, 100 mmol) at rt for 2 hours. The reaction mixture was filtered. The filtrate was concentrated, and then dissolved in EtOAc and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated to give the product (21.6 g, 91.5%). ^1H NMR (CDCl_3) δ 7.32-7.12 (m, 5H), 4.09 (s, 2H), 3.79-3.76 (m, 2H), 2.56 (d, J = 7.0 Hz, 2H), 1.89-1.80 (m, 1H), 1.79-1.71 (m, 4H), 1.28-1.12 (m, 2H).

Preparation of 1*N*-(4-benzylpiperidino)carbonylmethylamine.

To a solution of 1*N*-(4-benzylpiperidino)carbonylmethylchloride (3.3 g, 14 mmol) in acetone (48 mL) and water (32 mL) was added NaN_3 (1.4 g, 21 mmol), and the resulting mixture was refluxed for 16 hours. The mixture was concentrated, and the resulting aqueous solution was extracted with EtOAc. The organic layer was

dried over MgSO_4 and concentrated to give an azide intermediate as an oil. The oil was dissolved in MeOH (200 mL) and treated with hydrogen in the presence of 5% Pd on carbon for 16 hours. The mixture was filtered, and the
5 filtrate was concentrated to give the desired product (2.8 g, 82% for the two steps) as a colorless oil. ^1H NMR (CDCl_3) δ 7.28 (d, $J = 7.8$ Hz, 2H), 7.20 (dd, $J = 7.3$ Hz, $J = 7.0$ Hz, 1H), 7.13 (d, $J = 7.0$ Hz, 2H), 4.59 (d, $J = 10.3$ Hz, 1H), 3.74-3.61 (m, 1H), 3.46 (d, $J = 14.6$ Hz, 2H), 2.89 (t, $J =$
10 12.4 Hz, 1H), 2.59-2.54 (m, 2H), 1.91-1.68 (m, 6H), 1.17-1.13 (m, 2H); MS(CI) m/z 233 ($\text{M}+\text{H}$).

Preparation of 4-cyano-2-nitro-1N-(1'-N-(4-benzylpiperidino)carbonylmethyl)aniline.

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A solution of 4-cyano-2-nitro-benzenechloride (1.82 g, 10 mmol), 1N-(4-benzylpiperidino)carbonylmethylamine (2 g, 8.6 mmol) and NaHCO_3 (0.84 g, 10 mmol) in DMF (10 mL) was stirred at 100°C for 16 hours. The mixture was cooled to rt, diluted
20 with EtOAc (150 mL), and filtered. The residue was washed with water and EtOAc, and dried by air to give the product (1.6 g, 49.2%) as a golden solid. The filtrate was washed with 1N HCl, water and brine, dried over MgSO_4 , and concentrated to give more of the same product (1.1 g, 29%).
25 ^1H NMR (CDCl_3) δ 9.33 (s, 1H), 8.55 (d, $J = 1.5$ Hz, 1H), 7.63 (d, $J' = 8.8$ Hz, 1H), 7.33-7.20 (m, 3H), 7.14 (d, $J = 7.0$ Hz, 2H), 6.78 (d, $J = 9.1$ Hz, 1H), 4.65 (d, $J = 13.5$ Hz, 1H), 4.07 (d, $J = 3.7$ Hz, 2H), 3.71 (d, $J = 12.8$ Hz, 1H), 3.07 (t, $J =$
12.8 Hz, 1H), 2.67 (t, $J = 12.8$ Hz, 1H), 2.58 (t, $J = 6.3$ Hz,
30 2H), 1.85-1.95 (m, 3H), 1.22 (q, $J = 12.5$ Hz, 2H); MS(CI) m/z 379 ($\text{M}+\text{H}$).

Preparation of 2-amino-4-cyano-1N-(1'-N-(4'-benzylpiperidino)carbonylmethyl)aniline.

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A solution of 4-cyano-2-nitro-1N-(1'-N-(4'-benzylpiperidino)carbonylmethyl)aniline (1.6 g, 4.23 mmol) in MeOH (120 mL) was treated with hydrogen in the presence of 5%

Pd on carbon (0.2 g) for 16 hours. The mixture was filtered, and the filtrate was concentrated, followed by purification by CC with CH₂Cl₂, to give the product (1.33 g, 90%). ¹H NMR (CDCl₃) δ 7.26-7.03 (m, 6H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 5.10 (bs, 1H), 4.54 (d, *J* = 12.8 Hz, 1H), 3.86 (d, *J* = 4.5 Hz, 2H), 3.74 (s, 1H), 3.65 (d, *J* = 12.8 Hz, 1H), 3.61 (s, 1H), 3.03 (t, *J* = 12.8 Hz, 1H), 2.61 (d, *J* = 12.8 Hz, 1H), 2.53-2.51 (m, 2H), 1.80-1.65 (m, 3H), 1.35-1.05 (m, 2H); MS(CI) *m/z* 349 (M+H).

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Preparation of 5-cyano-1*N*-(1'*N*-(4'-benzylpiperidino)carbonylmethyl)-benzoimidazolinone.

A solution of 2-amino-4-cyano-1*N*-(1'*N*-(4'-benzylpiperidino)carbonylmethyl)aniline (320 mg, 0.94 mmol) in THF (10 mL) was treated with 1,1'-carbonyldiimidazole (162 mg, 1 mmol) at rt for 4 hours. The mixture was diluted with EtOAc (100 mL) and washed with brine (50 mL). The organic layer was dried over MgSO₄ and concentrated to give a crude, which was purified on TLC plates with 20% EtOAc in CH₂Cl₂ to give the product (303 mg, 86.2%). ¹H NMR (CDCl₃) δ 7.38-7.12 (m, 7H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.69 (dd, *J* = 24.2 Hz, *J* = 16.8 Hz, 2H), 4.55 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.5 Hz, 1H), 3.49 (s, 1H), 3.11 (t, *J* = 13.2 Hz, 1H), 2.61-2.58 (m, 3H), 1.83-1.72 (m, 3H), 1.26-1.21 (m, 2H); MS(CI) *m/z* 375.3 (M+H).

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Preparation of 5-amidino-1*N*-(1'*N*-(4'-benzylpiperidino)carbonylmethyl)-benzoimidazolinone.

By using of Pinner conditions followed by purification on HPLC, 5-cyano-1*N*-(1'*N*-(4'-benzylpiperidino)carbonylmethyl)benzoimidazolinone (300 mg, 0.8 mmol) was converted to the product (195 mg, 62.5%). ¹H NMR (CD₃OD) δ 7.54 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.29-7.14 (m, 6H), 4.94 (d, *J* = 17.1 Hz, 1H), 4.85 (d, *J* = 17.1 Hz, 1H), 4.42 (d, *J* = 13.2 Hz, 1H), 4.02 (d, *J* = 13.7 Hz, 1H), 3.12 (td, *J* = 13.4 Hz, *J* = 2.3 Hz, 1H), 2.64 (td, *J* = 13.3 Hz, *J* = 2.3 Hz, 1H), 2.58 (d, *J* = 7.1 Hz, 2H);

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1.93-1.81 (m, 1H), 1.78 (d, $J = 13.4$ Hz, 1H), 1.68 (d, $J = 12.7$ Hz, 1H); 1.39-1.29 (qd, $J = 12.7$ Hz, $J = 4.0$ Hz, 1H), 1.15 (qd, $J = 12.7$ Hz, $J = 4.0$ Hz, 1H); MS(ES) m/z 392.3 (M+H); HRMS:(M+H) calcd. for $C_{22}H_{25}N_5O_2$ 392.2087, found 392.2071; Anal.: ($C_{22}H_{25}N_5O_2 + 1.0TFA + 0.07HCl$).

Example 5

1N-(2'-Aminosulfonyl-[1,1']biphenylamino)carbonylmethyl-3N- β -hydroxyethylene-6-amidinobenzimidazolinone

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Preparation of 3-amino-4N-(β -hydroxyethylene)aminobenzonitrile.

A solution of 4-chloro-3-nitrobenzonitrile (18.3 g, 100 mmol), β -hydroxyethyleneamine (15 g, 245 mmol) and $NaHCO_3$ (8.4 g, 100 mmol) in MeOH (200 mL) was refluxed for 16 hours. The mixture was treated with hydrogen gas in the presence of 10% Pd on carbon (0.5 g) in MeOH (20 mL) for two days. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was partitioned in EtOAc and water. The organic layer was neutralized with 1N HCl to pH 7, and then washed with brine, dried over $MgSO_4$, and concentrated to give the product (16 g, 90.4% for the two steps). MS(CI) m/z 178 (M+H); 1H NMR (CD_3OD) δ 7.00 (dd, $J = 8.4$ Hz, $J = 1.8$ Hz, 1H), 6.89 (d, $J = 2.2$ Hz, 1H), 6.58 (d, $J = 8.4$ Hz, 1H), 3.75 (t, $J = 5.6$ Hz, 2H), 3.28 (t, $J = 5.5$ Hz, 2H).

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Preparation of 1N- β -hydroxyethylene-5-cyanobenzoimidazolinone.

After a solution of 3-amino-4N-(β -hydroxyethylene)aminobenzonitrile (6 g, 33.7 mmol) in THF (300 mL) was added slowly into a solution of 1,1'-carbonyldiimidazole (6 g, 37 mmol) in THF (200 mL), the resulting mixture was stirred at rt for 24 hours. The mixture was concentrated and the residue was dissolved in EtOAc (300 mL) and water (100 mL). The organic layer was washed with 1N HCl (50 mL), water (50 mL x 2) and brine (30 mL x 2), dried

over MgSO₄, and concentrated to give the product (5.9 g, 100%). MS(CI) *m/z* 204 (M+H); ¹H NMR (CD₃OD) δ 7.26 (dd, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 1.5 Hz, 1H), 6.94 (dd, *J* = 8.1 Hz, *J* = 1.8 Hz, 1H), 4.53 (t, *J* = 8.0 Hz, 2H), 3.93 (t, *J* = 8.0 Hz, 2H).

Preparation of 1*N*-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl-3*N*-β-hydroxyethylene-6-amidinobenzimidazolinone.

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To a solution of 1*N*-β-hydroxyethylene-5-cyanobenzoimidazolinone (100 mg, 0.5 mmol) in acetone (5 mL) was added K₂CO₃ (138 mg, 1 mmol), NaI (75 mg, 0.5 mmol), and *N*-(2'-*tert*-butylaminosulfonyl-[1,1']-biphenylamino)-carbonylmethylchloride (190 mg, 0.5 mmol). After being refluxed for 16 hours, the mixture was diluted with EtOAc (100 mL), washed with water (x2) and brine (x2), dried over MgSO₄, and concentrated to give a crude product of the nitrile intermediate. The nitrile was directly carried out in a Pinner reaction, followed by HPLC purification, to give the title compound (130 mg, 51% for the two steps). ¹H NMR (CD₃OD) δ ; 8.08 (dd, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.59-7.45 (m, 5H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 4.0 Hz, *J* = 1.5 Hz, 1H), 7.31 (d, *J* = 4.0 Hz, 1H), 4.62 (t, *J* = 7.7 Hz, 2H), 4.13 (s, 2H), 4.09 (t, *J* = 7.7 Hz, 2H); ESMS: *m/z* 509.4 (M+H)⁺.

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Example 6

1*N*-(1'*N*-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl)-6-amidinobenzoxazolinone

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Preparation of 3-amino-4-hydroxybenzonitrile.

A solution of 4-hydroxy-3-nitrobenzonitrile (10 g, 61 mmol) in MeOH (200 mL) was treated with hydrogen gas through a balloon in the presence of 5% Pd on active carbon (0.5 g) at room temperature for 24 hours. The mixture was filtered, and

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the filtrate was concentrated to give the product (8.2 g, 100%).

Preparation of 6-cyanobenzoxazolinone.

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To a solution of 3-amino-4-hydroxybenzonitrile (8.2 g, 61 mmol) in THF (200 mL) was added 1,1'-carbonyldiimidazole (11.6g, 72 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The reaction was then quenched with
10 1N HCl (50 mL), and the mixture was extracted with EtOAc (200 mL). The organic layer was washed with brine, dried over MgSO₄, and concentrated to give 6-cyanobenzoxazolinone (9.8 g, 100%). ¹H NMR (CDCl₃) δ 7.49 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 0.9 Hz, 1H).
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Preparation of 1N-(1'-N-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl-6-amidinobenzoxazolinone.

20 A mixture of 6-cyanobenzoxazolinone (160 mg, 1mmol), 1N-(2'-tert-butylaminosulfonyl-[1,1']-biphenylamino)carbonylmethylene chloride (380 mg, 1 mmol), NaI (75 mg, 0.5 mmol), and K₂CO₃ (207 mg, 1.5 mmol) in acetone (10 mL) was refluxed for 4 hours. The mixture was neutralized
25 with 1N HCl to pH 7 and extracted with EtOAc (200 mL). The organic layer was washed with brine, dried over MgSO₄, and concentrated to give a crude. The crude underwent a Pinner reaction, followed by HPLC purification, to give the title product (232 mg, 50%). ¹H NMR (CD₃OD) δ: 8.12 (dd, *J* = 7.7
30 Hz, *J* = 1.8 Hz, 1H), 7.92 (d, *J* = 1.2 Hz, 1H), 7.69 (td, *J* = 7.7 Hz, *J* = 2.2 Hz, 1H), 7.62 (dd, *J* = 7.3 Hz, *J* = 1.1 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 4.60 (s, 2H); ¹³C NMR (DMSO-*d*₆) δ 169.12, 164.26, 158.60,
35 154.17, 142.25, 139.74, 139.01, 132.49, 131.54, 131.17, 129.75, 129.50, 127.93, 127.33, 125.52, 123.78, 118.42, 117.24, 51.69; ESMS: *m/z* 466.4 (M+H)⁺; HRMS: (M+H) calcd. for C₂₂H₂₀N₅O₅S₁ 466.1185, found 466.1157.

Example 7**1N-(N-p-(4'-oxazolyl)phenylamino)carbonylmethyl-6-amidino-benzoxazolinone**

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Preparation of 1N-(N-p-(4'-oxazolyl)phenylamino)carbonylmethyl-6-cyano-benzoxazolinone.

A mixture of 6-cyanobenzoxazolinone (160 mg, 1mmol), p-(4-oxazolyl)phenyl chloroacetamido (380 mg, 1 mmol), NaI (150 mg, 1 mmol), and K₂CO₃ (138 mg, 1 mmol) in acetone (10 mL) was refluxed for 24 hours and then quenched with water (10 mL). The mixture was filtered, and the residue was collected and dried to give a crude product (400 mg). ¹H NMR (CDCl₃) δ 7.91 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 1.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.37 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 7.29 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.44 (s, 2H).

Preparation of 1N-(N-p-(4'-oxazolyl)phenylamino)carbonylmethyl-6-amidino-benzoxazolinone.

A crude of 1N-(N-p-(4'-oxazolyl)phenylamino)carbonylmethyl-6-cyano-benzoxazolinone (1 mmol) was carried on in a Pinner reaction, followed by purification by HPLC, to give the product (100 mg, 26.5%): ¹H NMR (CD₃OD) δ 8.28 (s, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.69 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.60 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 4.57 (s, 2H); ESMS: m/z 378 (M+H)⁺; Anal.: (C₁₉H₁₅N₅O₄ + 0.4TFA + 0.85HCl + 3H₂O).

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Example 8**1N-(1'-N-(4'-N-benzylsulfonylpiperazino)carbonylmethyl-6-amidino-benzoxazolinone**

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Preparation of N-benzylsulfonylpiperazine.

- Acylation of *N*-Boc-piperazine (1.86 g, 10 mmol) with benzylsulfonyl chloride (1.9 g, 10 mmol) in CH₃CN (20 mL) in the presence of Na₂CO₃ (1.01 g, 12 mmol) was carried out at rt for 16 hours. The mixture was diluted with EtOAc (150 mL), washed with water (50 mL), dried over MgSO₄, and concentrated to give 1*N*-Boc-4*N*-benzylsulfonyl-piperazine (3.3 g, 98%). ¹H NMR (CDCl₃) δ 7.39 (bs, 5H), 4.23 (s, 2H), 3.38-3.35 (m, 4H), 3.07-3.05 (m, 4H), 1.44 (s, 9H). The Boc-intermediate was deprotected with 4M HCl in dioxane (20 mL) at rt for 1 hour. The mixture was diluted with EtOAc, washed with 1*N* NaOH and water, dried over MgSO₄, and concentrated to give the product (1.9 g, 81%). ¹H NMR (CDCl₃) δ 7.46-7.43 (bs, 5H), 4.22 (s, 2H), 3.11-3.08 (m, 4H), 2.83-2.79 (m, 4H).
- Preparation of *N*-benzylsulfonylpiperazino-2-chloroacetamido.

- Acylation of *N*-benzylsulfonyl-piperazine (1.9 g, 7.9 mmol) with chloroacetyl chloride (1.13 g, 10 mmol) in CH₃CN (20 mL) in the presence of Na₂CO₃ (10 mmol) was carried out at rt for 2 hours. The mixture was diluted with EtOAc, washed with water, dried over MgSO₄, and concentrated to give the product (2.34 g, 95%). ¹H NMR (CDCl₃) δ 7.39 (bs, 5H), 4.26 (s, 2H), 4.02 (s, 2H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.45 (t, *J* = 4.8 Hz, 2H), 3.14-3.11 (m, 4H).

- Preparation of 1*N*-(1'*N*-(4'*N*-benzylsulfonylpiperazino)carbonylmethyl-6-amidino-benzoxazolinone.

- A mixture of 6-cyanobenzoxazolinone (80 mg, 0.5 mmol), *N*-benzylsulfonylpiperazino-2-chloroacetamido (158 mg, 0.5 mmol), and K₂CO₃ (138 mg, 1 mmol) in acetone (5 mL) was refluxed for 5 hours. The mixture was diluted with EtOAc, washed with water, and dried over MgSO₄. Concentration gave a crude, which was purified on TLC plates to give the cyano precursor. The cyano precursor was carried on in a Pinner reaction, followed by purification by HPLC, to give the product (56 g, 20% for two steps). ¹H NMR (DMSO-*d*₆) δ 9.31 (bs, 1.5H), 9.07

(bs, 1.5H), 7.69 (d, $J = 1.5$ Hz, 1H), 7.64 (d, $J = 8.3$ Hz, 1H), 7.59 (dd, $J = 8.8$ Hz, $J = 1.8$ Hz, 1H), 7.44-7.37 (m, 5H), 4.90 (s, 2H), 4.48 (s, 2H), 3.57 (bs, 2H), 3.47 (bs, 2H), 3.24 (bs, 2H), 3.15 (bs, 2H); ^{13}C NMR (DMSO- d_6) δ 165.26, 163.88, 153.90, 145.37, 132.03, 130.94, 129.31, 128.43, 128.30, 124.17, 123.29, 110.11, 109.43, 54.79, 45.38, 45.08, 44.14, 43.35, 41.62, 40.41; ESMS: m/z 458.2 ($M+H$) $^+$; HRMS: ($M+H$) calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_5\text{O}_5\text{S}_1$ 458.1498, found 458.1516.

Example 9

7-amidino-1N-(4'-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one

Preparation of 7-cyano-3,4-dihydroquinoxalin-2(1H)-one.

To a solution of 4-chloro-3-nitrobenzonitrile (18.3 g, 100 mmol) and glycine methyl ester·hydrochloride (12.3 g, 100 mmol) in EtOH (150 mL) was added NaHCO_3 (25.2 g, 300 mmol), and the resulting mixture was refluxed for 16 hours. The mixture was filtered and the filtrate was concentrated. The resulting residue was partitioned in EtOAc and water. The organic layer was neutralized with 1N HCl to pH 7 and then washed with brine, dried over MgSO_4 , and concentrated to give a crude (25 g). A solution of the crude was hydrogenated in MeOH (500 mL) in the presence of 10% Pd on carbon (1.5 g) at room temperature for 6 hours. The mixture was filtered and the filtrate was concentrated to give more of the same product (19.5 g, 100%). ^1H NMR (DMSO- d_6) δ 10.50 (s, 1H), 7.15 (dd, $J = 8.1$ Hz, $J = 1.8$ Hz, 1H), 6.94 (d, $J = 1.6$ Hz, 1H), 6.93 (s, 1H), 6.68 (d, $J = 8.4$ Hz, 1H), 3.90 (d, $J = 1.1$ Hz, 2H); MS(CI) m/z 191 ($M+\text{NH}_4$).

Preparation of 7-cyano-1N-(p-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

To a solution of 7-cyano-3,4-dihydroquinoxalin-2(1H)-one (4 mg, 20 mmol) in THF (100 mL) was added K_2CO_3 (152 mg, 1.1 mmol), 18-crown-6 (230 mg), and 2,4'-dibromoacetophenone (5.54

g, 20 mmol), and the resulting mixture was stirred for 16 hours. The mixture was diluted with EtOAc and filtered. The residue was washed with EtOAc and water, and dried by air to give the product (2.8 g, 37.8%). The filtrate was washed with
5 brine (50 mL x 4), dried over MgSO₄, and concentrated to give a crude material, which was recrystallized in EtOAc (20 mL) to give the product (2 g, 27%) as a white solid. ¹H NMR (DMSO-d₆) δ 8.02 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 1.4 Hz, 1H), 7.26 (dd, J = 8.1 Hz, J = 1.4 Hz, 1H),
10 7.10 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 4.05 (d, J = 1.1 Hz, 2H); MS(CI) m/z 370/372 (M+H).

Preparation of 7-amidino-1N-(4'-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

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MP: 145-150°C; MS(ES): m/z 385/387 (M+H); HRMS: (M+H) calcd. for C₁₇H₁₅N₄O₂Br 389.0436, found 389.0418; Anal.: (C₁₇H₁₅N₄O₂Br₁+1TFA+HCl) C, H, N, F, Cl; ¹H NMR (CD₃OD) δ 8.02 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.40 (dd, J =
20 8.4 Hz, 1H), 7.11 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 4.10 (s, 2H).

Example 10

7-amidino-1N-(3'-amino-[1,1']biphenyl)carbonyl-methyl-3,4-
25 dihydroquinoxalin-2(1H)-one

Preparation of 7-cyano-1N-(3'-amino-[1,1']-biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

30 A mixture of 7-cyano-1N-(p-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one (370 mg, 1 mmol), 3-aminophenyboronic acid (137 mg, 1 mmol), NaHCO₃ (210 mg, 2 mmol), and Pd(PPh₃)₄ (60 mg) in THF (10 mL) and water (1 mL) was refluxed under nitrogen for 16 hours. The mixture was
35 filtered, and the residue was washed with water, CH₂Cl₂, and dried by air to give the product (310 mg, 81.6 %). MS(ES): m/z 383.2 (M+H); ¹H NMR (CD₃OD) δ 8.22 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.63-7.58 (m,

2H), 7.34 (dd, $J = 8.4$ Hz, $J = 1.4$ Hz, 1H), 7.22 (dd, $J = 8.4$ Hz, $J = 1.4$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 5.54 (s, 2H), 4.08 (s, 2H)

- 5 Preparation of 7-amidino-1*N*-(3'-amino-[1,1']-biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

By using the general procedure of Pinner reaction, followed by HPLC purification, the product (157 mg, 50%) was
10 obtained from its cyano precursor (300 mg, 0.78 mmol). MP: 85°C; MS(ES): m/z 200.8 (M+H)²⁺; HRMS: (M+H) calcd. for C₂₃H₂₁N₅O₂ 400.1774, found 400.1780; ¹H NMR (CD₃OD) δ 8.21 (d, $J = 8.4$ Hz, 2H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.51-7.40 (m, 4H), 7.20-7.15 (m, 1H), 7.15 (dd, $J = 2.2$ Hz, 1H), 6.88 (d, $J = 8.4$
15 Hz, 1H), 5.56 (s, 2H), 4.12 (s, 2H).

Example 11

7-amidino-1*N*-(4'-fluoro-[1,1']biphenyl)carbonyl-methyl-3,4-dihydroquinoxalin-2(1H)-one

20

Preparation of 7-cyano-1*N*-(4'-fluoro-[1,1']-biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

A mixture of 7-cyano-1*N*-(*p*-bromophenyl)carbonylmethyl-
25 3,4-dihydroquinoxalin-2(1H)-one (370 mg, 1 mmol), 4-fluorophenylboronic acid (137 mg, 1 mmol), NaHCO₃ (210 mg, 2 mmol), and Pd(PPh₃)₄ (60 mg) in THF (10 mL) and water (1 mL) was refluxed under nitrogen for 16 hours. The mixture was filtered, and the filtrate was diluted with EtOAc (100 mL).
30 The organic layer was dried with MgSO₄, filtered, and concentrated to give a crude product (340 mg, 88.1%). MS(ES): m/z 386 (M+H); ¹H NMR (CDCl₃) δ 8.13 (d, $J = 8.1$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.63 (dq, $J = 8.8$ Hz, $J = 2.3$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 2H), 6.75 (s, 1H), 5.41 (s, 2H), 4.19 (s, 2H).
35

Preparation of 7-amidino-1*N*-(4'-fluoro-[1,1']-biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

By using Pinner conditions, followed by HPLC purification, the cyano precursor (300 mg, 0.80 mmol) was converted to the product (120 mg, 37%) MP: 138-140°C;
5 MS(ES): m/z 403 (M+H); ^1H NMR (CD_3OD) δ 8.19 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.73 (dq, J = 5.3 Hz, J = 2.1 Hz, 2H), 7.41 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 7.22 (td, J = 8.4 Hz, J = 2.2 Hz, 2H), 7.15 (d, J = 2.2 Hz, 1H), 5.57 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (CD_3OD) δ
10 192.51, 165.72, 145.43, 142.16, 135.74, 133.37, 128.85, 128.74, 128.64, 127.38, 126.88, 124.34, 115.60, 115.32, 113.80, 113.21, 48.48, 45.51; Anal.: ($\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_2\text{F}_1 + 1.2\text{TFA} + 0.05\text{HCl} + 1\text{H}_2\text{O}$) C, H, N, F, Cl.

15

Example 12**7-amidino-1N-[1,1']-biphenylcarbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one**

Preparation of 7-amidino-1N-[1,1']-biphenylcarbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.
20

A mixture of 7-cyano-1N-(p-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one (185 mg, 0.5 mmol), 4-phenyl-2'-bromoacetophenone (137 mg, 0.5 mmol), K_2CO_3 (210 mg, 2
25 mmol), and 18-crown-6 (20 mg) in THF (10 mL) was stirred for 16 hours. The mixture was filtered, and the filtrate was diluted with EtOAc (100 mL). The organic layer was dried with MgSO_4 , filtered, and concentrated to give a crude, which was carried on in a Pinner reaction, followed by HPLC
30 purification, to give the product (120 mg, 37%) as a solid. MP: 148-150°C; MS(ES): m/z 385.2 (M+H) $^+$; HRMS: (M+H) calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2$ 385.1664, found 385.1650; ^1H NMR (CD_3OD) δ 8.20 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 7.4 Hz, 2H), 7.47 (d, J = 7.7 Hz, 2H), 7.42-7.33 (m, 2H), 7.13
35 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.57 (s, 2H), 4.12 (s, 2H); ^{13}C NMR (CD_3OD) δ 192.51, 165.72, 145.43, 142.16, 135.74, 133.37, 128.85, 128.74, 128.64, 127.38,

126.88, 124.34, 115.60, 115.32, 113.80, 113.21, 48.48, 45.51;
Anal.: (C₂₃H₁₉N₄O₂F₁+1.2TFA+ 0.05HCl+1H₂O) C, H, N, F, Cl.

Examples 13 and 14

- 5 7-amidino-1N-(2'-tert-butylsulfonamido-
[1,1']biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one
(Example 13) and 7-amidino-1N-(2'-sulfonamido-[1,1']-
biphenyl)-carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one
(Example 14)

10

Preparation of 7-cyano-1N-(4'-sulfonamido-[1,1']-
biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one.

- A mixture of 7-cyano-1N-(p-bromophenyl)carbonylmethyl-
15 3,4-dihydroquinoxalin-2(1H)-one (370 mg, 1 mmol), o-tert-
butylsulfonamidophenyboronic acid (257 mg, 1 mmol), NaHCO₃
(210 mg, 2 mmol), and Pd(PPh₃)₄ (90 mg) in THF (20 mL) and
water (2 mL) was refluxed under nitrogen for 16 hours. The
mixture was filtered, and the filtrate was diluted with EtOAc
20 (100 mL). The organic layer was dried with MgSO₄, filtered,
and concentrated to give a crude, which was purified on TLC
plates to give the product (340 mg, 67.7%). MS(ES): m/z 503
(M+H); ¹H NMR (CDCl₃) δ 8.21 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H),
8.13 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.64-7.53
25 (m, 2H), 7.32 (dd, J = 8.4 Hz, J = 1.5 Hz, 1H), 7.23 (dd, J =
8.1 Hz, J = 1.5 Hz, 1H), 6.77 (d, J = 1.1 Hz, 1H), 6.74 (d, J
= 8.1 Hz, 1H), 5.30 (s, 2H), 4.21 (s, 2H), 3.63 (s, 1H), 1.08
(s, 9H).

- 30 Preparation of 7-amidino-1N-(2'-tert-butylsulfonamido-[1,1']-
biphenyl)-carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one and
7-amidino-1N-(2'-sulfonamido-[1,1']-biphenyl)carbonylmethyl-
3,4-dihydroquinoxalin-2(1H)-one.

- 35 By using the general procedure of Pinner reaction,
followed by HPLC purification, the cyano precursor (340 mg,
0.67 mmol) was converted to Example 13 (80 mg, 23%) and
Example 14 (120 mg, 38.7%), respectively. For Example 13:

HRMS: (M+H) calcd. for $C_{27}H_{30}N_5O_4S_1$ 520.2019, found 520.2013;
 1H NMR (CD_3OD) δ 8.16 (d, J = 8.8 Hz, 2H), 8.12 (dd, J = 1.4
 Hz, J = 1.4 Hz, 1H), 7.67-7.56 (m, 2H), 7.63 (d, J = 8.4 Hz,
 2H), 7.41 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H), 7.33 (dd, J = 7.7
 5 Hz, J = 1.4 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 6.88 (d, J =
 8.4 Hz, 1H), 5.58 (s, 2H), 4.13 (s, 2H), 1.07 (s, 9H); Anal.:
 ($C_{27}H_{30}N_5O_4S_1 + 1.1TFA + 0.5H_2O$) C, H, N, S, F, Cl; For Example
 14: HRMS: (M+H) calcd. for $C_{23}H_{21}N_5O_4S_1$ 464.1379, found
 464.1394; 1H NMR (CD_3OD) δ 8.16 (d, J = 8.8 Hz, 2H), 8.11 (d,
 10 J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.65-7.58 (m, 2H),
 7.41 (dd, J = 8.4 Hz, J = 2.2 Hz, 1H), 7.36 (dd, J = 7.3 Hz, J
 = 1.4 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 8.8 Hz,
 1H), 5.58 (s, 2H), 4.13 (s, 2H); ^{13}C NMR (CD_3OD) δ 194.11,
 167.16, 147.52, 143.64, 143.11, 140.84, 135.23, 133.09,
 15 132.95, 131.29, 129.44, 128.89, 128.71, 125.78, 116.77,
 115.20, 114.66, 54.77, 47.04.

Example 15

**1N-(2'-aminosulfonyl-[1,1']biphenylamino)carbonyl-methyl-7-
 20 amidino-3,4-dihydroquinoxalin-2(1H)-one**

Preparation of 1N-(2'-aminosulfonyl-[1,1']-
 biphenylamino)carbonylmethyl-7-amidino-3,4-dihydroquinoxalin-
 2(1H)-one.

25 A mixture of 7-cyano-3,4-dihydroquinoxalin-2(1H)-one (173
 mg, 1 mmol), K_2CO_3 (152 mg, 1.1 mmol), 18-crown-6 (15 mg), and
 1N-(2'-tert-butylaminosulfonyl-[1,1']-
 biphenylamino)carbonylmethyl chloride (380 mg, 1 mmol) in DMF
 30 (5 mL) was stirred at 80°C for 16 hours. The mixture was
 diluted with EtOAc, washed with brine (50 mL x 4), dried over
 $MgSO_4$, and concentrated to give a crude of the nitrile
 compound, which underwent a Pinner reaction and HPLC
 purification, to give the product (210 mg, 44% for the two
 35 steps). ESMS: m/z 479.2 (M+H); HRMS: (M+H) calcd. for
 $C_{23}H_{23}N_6O_4S_1$ 479.1502, found 479.1491; 1H NMR ($DMSO-d_6$) δ 10.34
 (s, 1H), 8.93 (s, 2H), 8.56 (s, 2H), 8.02 (d, J = 7.8 Hz, 2H),
 7.62-7.54 (m, 5H), 7.52 (td, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.34

(d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.2$ Hz, 1H), 5.18 (s, 1H), 4.80 (s, 2H), 4.06 (s, 2H), 3.51 (bs, 2H); ^{13}C NMR (CD_3OD) δ 168.44, 167.52, 156.97, 143.08, 141.54, 139.03, 137.37, 134.89, 133.66, 132.92, 132.70, 131.26, 128.73, 128.61, 123.56, 122.07, 120.58, 110.74, 108.96, 44.63

Example 16

6-amidino-1*N*-[1,1']-biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1*H*)-one

10

Preparation of 2*N*-Boc-amino-5-cyanophenylglycin ethyl ester.

To a solution of *N*-Boc-2-amino-5-cyanoaniline (4.66 g, 20 mmol) in DMF (80 mL) was added K_2CO_3 (2.76 g, 20 mmol), 18-crown-6 (0.3 g), and ethyl bromoacetate (3.5 g, 22 mmol). After the mixture was stirred at 70°C for 16 hours, it was cooled to rt, diluted with EtOAc, washed with water, and dried over MgSO_4 . Filtration and concentration, followed by purification by CC with 5% EtOAc in CH_2Cl_2 , provided the product (2.4 g, 41%). ^1H NMR (CDCl_3) δ 7.67 (d, $J = 8.4$ Hz, 1), 7.15 (dd, $J = 8.1$ Hz, $J = 1.8$ Hz, 1H), 6.86 (d, $J = 1.8$ Hz, 1H), 6.43 (bs, 1H), 4.29 (q, $J = 7.0$ Hz, 2H), 3.87 (d, $J = 5.5$ Hz, 2H), 1.53 (s, 9H), 1.33 (t, $J = 7.0$ Hz, 3H).

Preparation of 6-cyano-3,4-dihydroquinoxalin-2(1*H*)-one.

N-Boc-2-amino-5-cyanophenylglycin ethyl ester (2.6 g, 8.17 mmol) in MeOH (20 mL) was treated with 4*M* HCl in dioxane (20 mL) at rt for 16 hours. To the mixture was added Et_2O until no more solid appeared. The solid was collected, washed with Et_2O , and dried by air to give the product (1.4 g, 82 %). ^1H NMR (CD_3COCD_3) δ 7.02 (d, $J = 8.4$ Hz, 1H), 7.00 (d, $J = 1.8$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 3.89 (s, 2H).

Preparation of 6-amidino-1*N*-[1,1']-biphenylcarbonylmethyl-3,4-dihydroquinoxalin-2(1*H*)-one.

A mixture of 6-cyano-3,4-dihydroquinoxalin-2(1H)-one (171 mg, 0.82 mmol), 4-phenyl-2'-bromoacetophenone (277 mg, 1 mmol), K₂CO₃ (140 mg, 1 mmol), and 18-crown-6 (30 mg) in DMF (5 mL) was stirred for 16 hours. The mixture was diluted with EtOAc (160 mL) and water (40 mL). The organic layer was washed with brine, dried with MgSO₄, filtered, concentrated, and purified on TLC plates to give a 6-cyano-1N-(4'-phenylphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one (110 mg, 37%). The cyano precursor was carried on in a Pinner reaction, followed by HPLC purification, to give the product (30 mg, 26%) as a solid. HRMS: (M+H) calcd. for C₂₃H₂₀N₄O₂ 385.1651, found 385.1652; ¹H NMR (CD₃OD) δ 8.52 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.0 Hz, 2H), 7.51-7.41 (m, 3H), 7.15 (bs, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.57 (s, 2H), 4.07 (s, 2H).

Example 17

1N-[1,1']Biphenylcarbonyl)ethyl-6-amidinobenzoxazolinone

Preparation of 3-[1,1']-biphenyl-1,2-propen-3-one.

trans-Benzyl(chloro)*bis*-(triphenylphosphine)palladium(II) (0.24 mmol, 0.18g) and vinyltributyl tin (47.31 mmol, 15g) were added to a suspension of [1,1']-biphenylcarbonyl chloride (45.49 mmol, 9.82g) in 30mL chloroform. The reaction mixture was warmed to 60°C for ca. 15h. Then the reaction mixture was poured into diethyl ether and washed with water and half saturated KF solution. The tin salts were filtered the organics were dried over MgSO₄ and concentrated in vacuo. The crude material was purified by standard chromatographic technique to give the product as a white solid. LRMS: m/z 209 (M+H, 100). ¹H NMR (CDCl₃, 300MHz) δ 8.50 (d, 2H), 7.71 (d, 2H), 7.63 (d, 2H), 7.45 (m, 3H), 7.20 (m, 1H), 6.49 (dd, 1H), 5.95 (dd, 1H).

Preparation of 1N-([1,1']-biphenylcarbonyl)ethyl-6-amidinobenzoxazolinone.

6-Cyanobenzoxazolinone (5.0 mmol, 0.80g) was synthesized as previously described and added to a solution of 3-[1,1']-biphenyl-1,2-propen-3-one (5.0 mmol, 1.04g) and triethylamine (10.00 mmol, 1.39mL) in 40mL acetonitrile. The reaction mixture was warmed from ambient temperature to 77°C for 2h. The reaction mixture was concentrated and placed under high vacuum to give the crude product. The crude material was used directly. LRMS: m/z 386 (M+NH₄,100). The 1N-[[1,1']-biphenylcarbonyl]ethyl-6-cyanobenzoxazolinone was converted to its corresponding benzamidine via the Pinner synthesis and amidination with ammonium carbonate to give crude 1N-[4-biphenylcarbonyl]ethyl-6-amidinobenzoxazolinone. The crude product was purified by standard reverse phase HPLC. LRMS: m/z 386 (M+H,100). HRMS: calcd for C₂₃H₂₀N₃O₃, 386.150467; found, 386.150040.

Example 18

1-([1,1']-Biphenylcarbonyl)ethyl-6-amidino-3N-methylbenzimidazolinone

6-Cyano-3N-methylbenzimidazolone (2.31 mmol, 0.40g) which was synthesized similarly to its benzimidazolone analog except that 1N-methyl-2-amino-4-cyanoaniline was used as starting material and 3-(4-biphenyl)-1,2-propen-3-one (2.31 mmol, 0.48g) were combined in 20mL of acetonitrile to form a suspension. The reaction mixture was warmed to 77°C and heated for 24h. The reaction mixture was concentrated and the resulting residue was purified by standard chromatographic technique to give 1-(4-biphenylcarbonyl)ethyl-6-cyanobenzimidazolinone. LRMS: m/z 382 (M+H,100). The purified material was subjected to Pinner conditions followed by reaction with ammonium carbonate to give the title compound 1-(4-biphenylcarbonyl)ethyl-6-amidino-3N-methylbenzimidazolinone. ¹H NMR (CDCl₃, 300MHz): δ 9.12 (bs, 2H), 8.77 (bs, 2H), 8.01 (d, 2H), 7.78 (m, 3H), 7.72 (d, 2H), 7.43 (complex, 5H), 4.21 (t, 2H), 3.56 (t, 2H), 3.35 (s, 3H). LRMS: m/z 399.4 (M+H,100). HRMS: calcd for C₂₄H₂₃N₄O₂, 399.182101; found, 399.181375.

Example 19**1-([1,1']-biphenylcarbonyl)ethyl-6-amidinobenzimidazolinone**

5 6-Cyano-3N-acetylbenzimidazolone (1.47 mmol, 0.29g) which
was synthesized similarly to its benzimidazolone analog except
that 1N-acetyl-2-amino-4-cyanoaniline was used as starting
material and 3-(4-biphenyl)-1,2-propen-3-one (1.37 mmol,
0.29g) were combined in 15mL of acetonitrile to form a
10 suspension. The reaction mixture was warmed to 77°C and heated
for 24h. The reaction mixture was concentrated and the
resulting residue was purified by standard chromatographic
technique to give crude 1-(4-biphenylcarbonyl)ethyl-6-cyano-
3N-acetylbenzimidazolinone. The crude material was subjected
15 to Pinner conditions followed by reaction with ammonium
carbonate to give the title compound 1-(4-
biphenylcarbonyl)ethyl-6-amidinobenzimidazolinone. LRMS: m/z
385 (M+H,100). HRMS: calcd for C₂₃H₂₁N₄O₂, 385.166451; found,
385.167149.

20

Example 20**1N-(4-Bromophenylcarbonyl)ethyl-6-amidinobenzoxazolinone**

Preparation of 1N-(4-Bromophenylcarbonyl)ethyl-6-
25 cyanobenzoxazolinone.

6-Cyanobenzoxazolinone (7.06 mmol, 1.13g) was synthesized
as previously described (Example 6) and added to a solution of
4-bromo-beta-chloropropiophenone (7.77 mmol, 1.92g) and
30 triethylamine (17.66 mmol, 2.46mL) in 100mL acetonitrile. The
reaction mixture was warmed to 77°C for 24h. The reaction
mixture was allowed to cool to ambient temperature at which
time the product precipitated from the solution as a white
solid. LRMS: m/z 390 (M+NH₄). The 1N-(4-
35 bromophenylcarbonyl)ethyl-6-cyanobenzoxazolinone was used
directly and was converted to its corresponding benzamidine
via the Pinner synthesis followed by amidination with ammonium
carbonate to give crude 1N-(4-bromophenylcarbonyl)ethyl-6-

amidinobenzoxazolinone. The crude product was purified by standard reverse phase HPLC. ^1H NMR(dms o-d_6 , 300MHz): δ 9.30 (bs, 2H), 9.10 (bs, 2H), 7.85 (m, 4H), 7.71 (d, 2H), 7.58 (s, 1H), 4.15 (t, 2H), 3.58 (t, 2H). LRMS: m/z 390 (M+H, 100).

5 HRMS: calcd for $\text{C}_{17}\text{H}_{14}\text{BrN}_3\text{O}_3$, 388.029678; found, 388.030885.

Example 21

1N-[4-(2-Aminosulfonylphenyl)pyridin-2-yl]aminocarbonylmethyl-6-amidinobenzoxazolinone

10

Preparation of 2-Aminocarbonylmethylchloro-4-(2'-tert-butylsulphonylphenyl)pyridine.

15 Chloroacetyl chloride (8.23 mmol, 0.66mL) was dripped into a solution of 2-amino-5-(2'-tert-butylsulphonylphenyl)pyridine (8.23mmol, 2.51g) in 80mL THF. The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure to give 2-aminocarbonylmethylchloro-5-(2'-tert-butylsulphonylphenyl)pyridine as white solid. LRMS: m/z 382 (M+H).

25 Preparation of 1N-[4-((2'-tert-Butylaminosulphonylphenyl)pyridin-1-yl)aminocarbonylmethyl]-6-amidinobenzoxazolinone.

30 6-Cyanobenzoxazolinone (5.33 mmol, 0.85g) was added to a solution of 2-aminocarbonylmethylchloro-5-(2'-tert-butylaminosulphonylphenyl)pyridine (5.33 mmol, 2.22g), sodium iodide (2.67 mmol, 0.40g) and triethylamine (15.99 mmol, 2.23mL) in 50mL THF. The reaction mixture was warmed to reflux temperature for 24h. Then the reaction mixture was concentrated and purified via standard flash chromatographic technique to give 1N-[4-((2'-tert-butylaminosulphonylphenyl)pyridin-1-yl)aminocarbonylmethyl]-6-cyanobenzoxazolinone. LRMS: m/z 506 (M+H, 100). The 1N-[4-((2'-tert-butylaminosulphonylphenyl)pyridin-1-yl)aminocarbonylmethyl]-6-cyanobenzoxazolinone was converted

to its corresponding benzamidine via the Pinner synthesis and amidination with ammonium carbonate to give crude 1N-[5-((2'-tert-butylsulphonylphenyl)pyridin-1-yl)aminocarbonylmethyl]-6-amidinobenzoxazolinone. The crude product was purified by standard reverse phase HPLC. ¹H NMR (DMSO-d₆, 300MHz): δ 11.21 (s, 1H), 9.26 (s, 2H), 8.91 (s, 2H), 8.30 (d, 1H), 7.98 (m, 2H), 7.77 (m, 2H), 7.62 (m, 3H), 7.36 (m, 2H), 4.82 (bs, 2H). LRMS: m/z 467(M+H). HRMS: calcd for C₂₁H₁₇N₆O₄, 467.113765; found, 467.114384.

10

Example 22

1N-(4-Morpholinosulfonamidophenyl)aminocarbonylmethyl-6-amidinobenzoxazolinone

15 Preparation of 4-Nitrobenzenemorpholinosulfonamide.

Morpholine (44.31 mmol, 3.86mL) was dripped into a cooled (0°C) solution of 4-nitrobenzenesulfonyl chloride (14.77 mmol, 3.27g) in 100mL methylene chloride. The reaction mixture was allowed to warm to ambient temperature overnight. Then the reaction mixture was concentrated under reduced pressure and diluted with EtOAc. The organics were washed 3x50mL water, dried over MgSO₄ and concentrated in vacuo to give a yellow solid. The crude 4-nitrobenzenemorpholinesulfonamide was used directly after a few hours under high vacuum. LRMS: m/z 290(M+NH₄). The crude nitro compound was reduced catalytically with 10% palladium on carbon at 1 atm of hydrogen to give 0.43 g of crude 4-morpholinesulfonamidoaniline. LRMS: m/z 243 (M+H, 100).

30

Preparation of 4-Aminocarbonylmethylchlorobenzenemorpholinosulfonamide.

Chloroacetyl chloride (1.78 mmol, 0.14mL) was dripped into a solution of 4-morpholinesulfonamidoaniline (1.78 mmol, 0.43g) and triethylamine (3.73 mmol, 0.52mL) in 100mL THF. The reaction mixture was stirred for 20h at ambient temperature. The reaction mixture was concentrated under

reduced pressure and worked up with water and brine washings to give the crude 4-aminocarbonylmethylchlorobenzenemorpholinesulfonamide. LRMS: m/z 319 (M+H).

5

Preparation of 1N-(4-Morpholinosulfonamidophenyl)carbonylmethyl-6-amidinobenzoxazolinone.

10 6-Cyanobenzoxazolinone (0.82mmol, 0.13g) was added to a solution 4-aminocarbonylmethylchlorobenzenemorpholinesulfonamide (0.82 mmol, 0.26g) and triethylamine (1.80 mmol, 0.25mL) in 10mL acetonitrile. The reaction mixture was warmed to 80°C for 24h.
15 Then the reaction mixture was concentrated and purified via standard flash chromatographic technique to give 1N-(4-morpholinesulfonamidophen-1-yl)aminocarbonylmethyl-6-cyanobenzoxazolinone. LRMS: m/z 460 (M+NH₄). The 1N-(4-morpholinesulfonamidophen-1-yl)aminocarbonylmethyl-6-cyanobenzoxazolinone was converted to its corresponding
20 benzamidine via the Pinner synthesis and amidination with ammonium carbonate to give the crude 1N-(4-morpholinesulfonamidophenyl)aminocarbonylmethyl-6-amidinobenzoxazolinone. The crude product was purified by
25 standard reverse phase HPLC. ¹H NMR (DMSO-d₆, 300MHz): δ 11.10 (s, 1H), 9.21 (bs, 2H), 8.72 (bs, 2H), 7.91 (m, 3H), 7.82 (m, 4H), 4.53 (s, 2H), 3.62 (m, 4H), 2.88 (m, 4H). LRMS: m/z 460 (M+H). HRMS: calcd for C₂₁H₂₁N₅O₆S, 460.130418; found, 460.130002.

30

Example 101

3-(3-methoxy-(2'-aminosulfonyl-[1,1']biphenyl-1-aminocarbonyl)methyl-5-amidino-2-indolinone

35 To a stirred solution of 3-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl-5-cyanoindole (300mg, 0.62mmol) in 10mL of t-BuOH was added NBS (120 mg, 0.67mmol) at rt and it stirred for 18h. The reaction was diluted with water and

extracted with ethyl acetate (3x), dried with sodium sulfate, filtered and concentrated in vacuo. The yellow residue was chromatographed via flash Silica Gel using 1:1 hexanes:ethylacetate as the eluant. Fractions were collected and concentrated in vacuo to afford of desired product in 35% yield (130mg, 0.22mmol). The bromo compound was then dissolved in dry MeOH cooled to -20°C and saturated with HCl(g). Resulting solution was allowed to warm up to rt over 18h. The reaction was concentrated in vacuo. The resulting residue was dissolved in dry MeOH and after addition of ammonium carbonate the flask sealed and stirred for 18 at rt. The mixture was filtered through Celite®, rinsed with MeOH, and methylene chloride. Concentration under vacuo afforded a mixture of products. Separation and purification was accomplished via prep. HPLC to afford the 3-methoxy, and the 3-amino 2-oxyindoles. ¹H NMR (CD₃OD) δ ppm 3.05 (s, 3H), 3.25 (qd, 2H, J= 15Hz), 7.21(d,1H, J= 7.5Hz), 7.32 (m, 3H), 7.51 (m, 4H), 7.82 (d, J=7.5Hz), 8.03, (m, 2H). HRMS (M+H)⁺ for C₂₄H₂₄N₅O₅S calc: 494.149816; found: 494.149536.

20

Example 102**3-(3-amino-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl-5-amidino-2-indolinone**

Prepared and purified using the procedure from Example 101. ¹H NMR (CD₃OD) δ ppm 3.25 (qd, 2H, J= 15Hz), 7.21(d,1H, J= 7.5Hz), 7.32 (m, 3H), 7.51 (m, 4H), 7.82 (d, J=7.5Hz), 8.03, (m, 2H). HRMS (M+H)⁺ for C₂₃H₂₃N₆O₄S calc: 479.148813; found: 479.149389.

30

Example 103**3-(3-hydroxy-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl-5-amidino-2-indolinone**

Preparation of 3-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl-5-cyanoindole.

To a stirred solution of 5-cyano-3-acetic acid indole (1.0g, 5.0mmol), BOP (3.32g, 7.5 mmol) in DMF (35mL) was added 4-(2-aminosulfonyl)phenyl-2-aminobenzene (1.48 mg, 6.0mmol) and heated at 50°C for 3h. The reaction was diluted with
5 water, extracted with ethyl acetate, washed with 10% HCl, sodium bicarbonate, brine, water, dried with magnesium sulfate, filtered and concentrated in vacuo to afford 420mg of product. The t-butyl group was removed in TFA reflux for 1h. Purified via silica gel using 100% ethyl acetate as the eluent
10 to afford 530 mg of product. LRMS (M+H)⁺ 431.

Preparation of 3-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl-5-amidinoindole.

15 The 5-cyanoindole was subjected to the Pinner conditions followed by ammonium carbonate in dry MeOH. Purification was accomplished via prep HPLC to afford 264 mg of product. HRMS calc 448.14337; found 448.142583.

20 Preparation of 2-[3-(3-hydroxy-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl)-5-amidino-2-indolinone.

To a stirred solution of 3-(2'-aminosulfonyl-[1,1']-biphenylaminocarbonyl)methyl-5-amidinoindole (1.03g, 2.1mmol)
25 in 30 mL of t-BuOH was added NBS (374mg, 2.1mmol) and stirred for 18h at rt under a nitrogen atmosphere. The mixture was concentrated in vacuo and redissolved in dry MeOH/MeOAc (1:4) Ammonium carbonate (x's) was added the flask sealed and stirred at rt for 48h. Resulting mixture was filtered through
30 Celite®, rinsed with MeOH and methylene chloride and the filtrate was concentrated in vacuo. Purification was accomplished via prep HPLC to afford 60mg of desired product as the TFA salt. ¹H NMR (DMSO-d₆) δ ppm 3.05 (q, 2H, J=11.5 Hz), 6.98 (d, 1H, J=6.0 Hz) 7.18 (s, 2H), 7.22 (m, 3H), 7.41
35 (d, 1H, J= 6.0Hz), 7.40 (s, 1H), 7.58 (m, 2H), 7.75 (d, 1H, J=6.0Hz), 7.82 (s, 1H), 8.0 (d, 1H, J= 6.0Hz) 8.67 (bs, 2H), 9.15 (bs, 2H), 10.05 (bs, 1H), 10.78 (s, 1H). HRMS (M+H)⁺ for C₂₃H₂₂N₅O₅S calc:480.134166; found: 480.135777.

Example 104

3-(3'-hydroxy-(2-chloro-(2'-aminosulfonyl)-[1,1']-biphenylaminocarbonyl)methyl-5-amidino-2-indolinone

5

Prepared using the procedure of Example 103. ¹H NMR (CD₃OD) δ ppm 3.25 (qd, 2H, J=9 Hz), 7.04 (d, 1H, J=9 Hz), 7.23 (m, 2H), 7.43 (nd, 1H, J=1.8 Hz), 7.58 (m, 3H), 7.78 (dd, 1H, J=1.8 Hz, J=9.0 Hz), 7.83 (nd, 1H, J=1.8 Hz), 8.04 (dd, 1H, J=1.8 Hz, J=9.0 Hz). HRMS (M+H)⁺ for C₂₃H₂₁ClN₅O₅S calc.: 514.095194; found: 514.094336.

10

Example 105

3-(3'-amino-(2-chloro-(2'-aminosulfonyl)-[1,1']-biphenylaminocarbonyl)methyl-5-amidino-2-indolinone

15

Isolated from the preparation of Example 104. ¹H NMR (CD₃OD) δ ppm 3.05 (qd, 2H, J=9.0 Hz), 7.09 (d, 1H, J= 6.0 Hz), 7.25 (t, 2H, J=6.0 Hz), 7.45 (m, 4H), 7.81 (d, 1H, J= 6.0 Hz), 8.03 (m, 2H). HRMS (M+H)⁺ for C₂₃H₂₁ClN₆O₄S calc.: 513.111178; found: 513.113281.

20

Example 201

3-(2-chloro-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl-5-amidino-2-indolinone

25

Isolated from the preparation of Example 104. ¹H NMR (CD₃OD) δ ppm 3.6 (s, 2H), 7.15 (d, 1H, J= 7.2 Hz), 7.23 (d, 1H, J= 4.8 Hz), 7.32 (1H, J=4.8 Hz), 7.5 (m, 5H), 7.81 (d, 1H, J=7.2 Hz), 8.03 (s, 1H). HRMS (M+H)⁺ for C₂₃H₁₉ClN₅O₄S calc.: 496.084629; found: 496.084051.

30

Example 202

3-(2-bromo-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl-5-amidino-2-indolinone

35

Prepared using the procedure of Example 201. ¹H NMR (CD₃OD) δ ppm 3.58 (s, 2H), 7.12 (d, 1H, J=9.0 Hz), 7.21 (d, 1H,

J= 7.2Hz), 7.36 (s, 2H), 7.58 (m, 2H), 7.8 (d, 1H, J= 9.0Hz), 8.03 (d, 1H, J=7.2Hz), 8.08 (s, 1H). HRMS (M+H)⁺ for C₂₃H₁₉BrN₅O₄S calc.: 540.03442; found: 540.032207.

5

Example 203

3-(2-fluoro-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl-5-amidino-2-indolinone

Prepared using the procedure of Example 201. ¹H NMR (CD₃OD) δppm 3.58 (q, 2H, J=9.0Hz), 7.04 (d, 1H, J=9.0Hz), 7.16 (d, 1H, J=7.2Hz), 7.21 (d, 1H, J=7.0Hz), 7.23 (d, 1H, J=7.0Hz), 7.58 (m, 3H), 7.81 (d, 1H, J=9.0Hz), 7.89 (s, 1H), 8.12 (m, 2H). HRMS (M+H)⁺ for C₂₃H₁₉FN₅O₄S calc.: 480.114179; found: 480.114566.

15

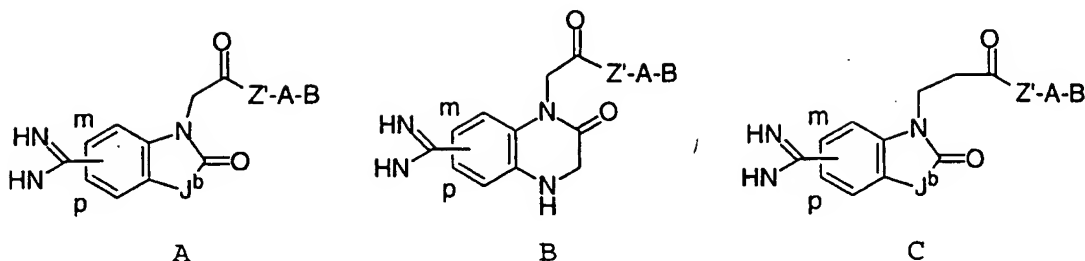
Example 204

3-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl-5-amidino-2-indolinone

Prepared using the procedure of Example 201. HRMS (M+H)⁺ for C₂₃H₂₀FN₅O₄S calc.: 462.123601; found: 462.123950.

20

Table 1



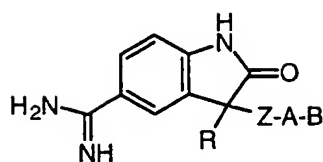
5

Ex #	Fig.	Am	J ^b	Z'-A-B	MS
1	A	m	NH	2'-aminosulfonyl-[1,1']-biphenylamino	465.1345
2	A	p	NH	2'-aminosulfonyl-[1,1']-biphenylamino	465.4
3	A	m	NH	4'-chlorophenyl-thiazol-2-yl	427.0743
4	A	p	NH	4'-benzylpiperidino	392.2071
5	A	m	N-(CH ₂) ₂ OH	2'-aminosulfonyl-[1,1']-biphenylamino	509.4
6	A	m	O	2'-aminosulfonyl-[1,1']-biphenylamino	466.1157
7	A	m	O	4-(oxazol-5'-yl)phenylamino	378
8	A	m	O	4'-(benzylsulfonyl)piperidino	458.1516
9	B	m	-	4'-bromophenyl	387.0286
10	B	m	-	2'-amino-[1,1']-biphenyl	400.1780
11	B	m	-	4'-fluoro-[1,1']-biphenyl	403
12	B	m	-	[1,1']-biphenyl	385.1650
13	B	m	-	2'-t-butylaminosulfonyl-[1,1']-biphenylamino	520.2013
14	B	m	-	2'-aminosulfonyl-[1,1']-biphenylamino	464.1396
15	B		NH	2'-aminosulfonyl-[1,1']-biphenylamino	479.1491
16	B	p	-	[1,1']-biphenyl	385.1651

17	C	m	O	[1,1']-biphenyl	386
18	C	m	NCH ₃	[1,1']-biphenyl	399
19	C	m	NH	[1,1']-biphenyl	385
20	C	m	O	4-bromophenyl	390
21	A	m	O	5-(2'-aminosulfonyl-phenyl)pyridin-2-ylamino	467
22	A	m	O	4-(morpholinosulfonyl)phenylamino	460

Unless otherwise defined, all stereochemistry is (+/-).

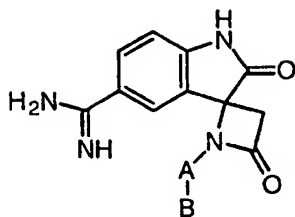
Table 2



Ex#	R	Z-A-B	MS
101	methoxy	2'-aminosulfonyl-[1,1']-biphenyl-aminocarbonylmethyl	494.1495
102	amino	2'-aminosulfonyl-[1,1']-biphenyl-aminocarbonylmethyl	479.1488
103	hydroxy	2'-aminosulfonyl-[1,1']-biphenyl-aminocarbonylmethyl	480.1358
104	hydroxy	2'-aminosulfonyl-2-chloro-[1,1']-biphenyl-aminocarbonylmethyl	514.0943
105	amino	2'-aminosulfonyl-2-chloro-[1,1']-biphenyl-aminocarbonylmethyl	513.1133

5 Unless otherwise defined, all stereochemistry is (+/-).

Table 3

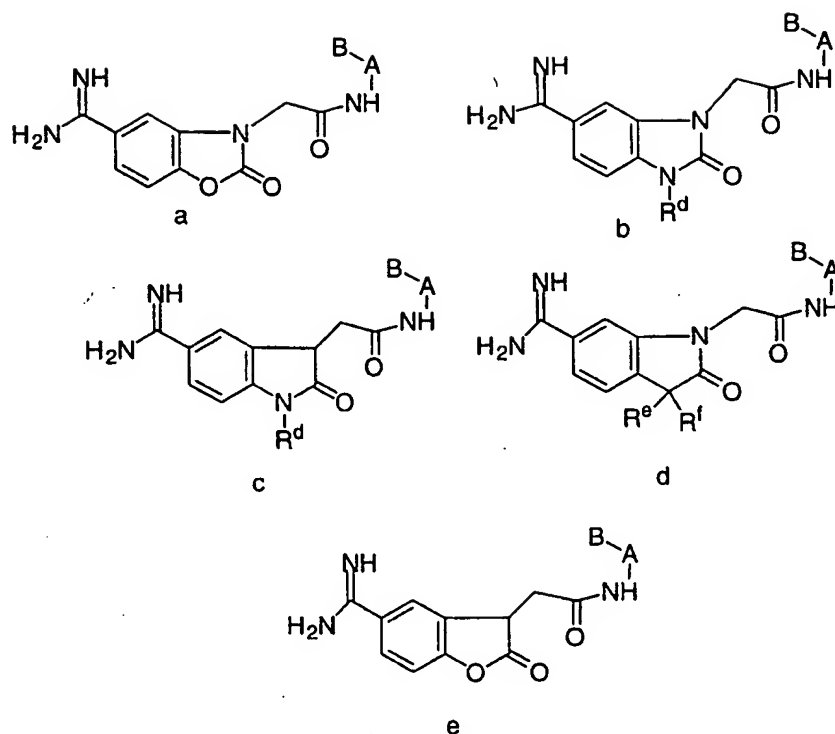


Ex#	A-B	MS
201	2'-aminosulfonyl-2-chloro-[1,1']-biphenyl-	496.0840
202	2'-aminosulfonyl-2-bromo-[1,1']-biphenyl-	540.03221
203	2'-aminosulfonyl-2-fluoro-[1,1']-biphenyl-	480.1146
204	2'-aminosulfonyl-2-[1,1']-biphenyl-	462.1230

5 Unless otherwise defined, all stereochemistry is (+/-).

The following table contains representative examples of the present invention. Each entry in the table is intended to be paired with each formulae at the start of the table.

Table 4



Ex #	A	B
301	phenyl	2-(aminosulfonyl)phenyl
302	phenyl	2-(methylaminosulfonyl)phenyl
303	phenyl	1-pyrrolidinocarbonyl
304	phenyl	2-(methylsulfonyl)phenyl
305	phenyl	4-morpholino
306	phenyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
307	phenyl	4-morpholinocarbonyl
308	2-pyridyl	2-(aminosulfonyl)phenyl
309	2-pyridyl	2-(methylaminosulfonyl)phenyl
310	2-pyridyl	1-pyrrolidinocarbonyl
311	2-pyridyl	2-(methylsulfonyl)phenyl
312	2-pyridyl	4-morpholino
313	2-pyridyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
314	2-pyridyl	4-morpholinocarbonyl
315	3-pyridyl	2-(aminosulfonyl)phenyl
316	3-pyridyl	2-(methylaminosulfonyl)phenyl
317	3-pyridyl	1-pyrrolidinocarbonyl
318	3-pyridyl	2-(methylsulfonyl)phenyl
319	3-pyridyl	4-morpholino
320	3-pyridyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
321	3-pyridyl	4-morpholinocarbonyl
322	2-pyrimidyl	2-(aminosulfonyl)phenyl
323	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
324	2-pyrimidyl	1-pyrrolidinocarbonyl
325	2-pyrimidyl	2-(methylsulfonyl)phenyl
326	2-pyrimidyl	4-morpholino

327	2-pyrimidyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
328	2-pyrimidyl	4-morpholinocarbonyl
329	5-pyrimidyl	2-(aminosulfonyl)phenyl
330	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
331	5-pyrimidyl	1-pyrrolidinocarbonyl
332	5-pyrimidyl	2-(methysulfonyl)phenyl
333	5-pyrimidyl	4-morpholino
334	5-pyrimidyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
335	5-pyrimidyl	4-morpholinocarbonyl
336	2-Cl-phenyl	2-(aminosulfonyl)phenyl
337	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
338	2-Cl-phenyl	1-pyrrolidinocarbonyl
339	2-Cl-phenyl	2-(methysulfonyl)phenyl
340	2-Cl-phenyl	4-morpholino
341	2-Cl-phenyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
342	2-Cl-phenyl	4-morpholinocarbonyl
343	2-F-phenyl	2-(aminosulfonyl)phenyl
344	2-F-phenyl	2-(methylaminosulfonyl)phenyl
345	2-F-phenyl	1-pyrrolidinocarbonyl
346	2-F-phenyl	2-(methysulfonyl)phenyl
347	2-F-phenyl	4-morpholino
348	2-F-phenyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
349	2-F-phenyl	4-morpholinocarbonyl
350	2,5-diF-phenyl	2-(aminosulfonyl)phenyl
351	2,5-diF-phenyl	2-(methylaminosulfonyl)phenyl
352	2,5-diF-phenyl	1-pyrrolidinocarbonyl
353	2,5-diF-phenyl	2-(methysulfonyl)phenyl
354	2,5-diF-phenyl	4-morpholino
355	2,5-diF-phenyl	2-(1'-CF ₃ -tetrazol-2-yl)phenyl
356	2,5-diF-phenyl	4-morpholinocarbonyl

Unless otherwise defined, all stereochemistry is (+/-).

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i .

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m , for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_0 - v_s) / v_s = I / (K_i (1 + S / K_m))$$

where:

v_0 is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

5 I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

10 Using the methodology described above, a number of compounds of the present invention were found to exhibit a K_i of $\leq 15 \mu M$, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group.

30 The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes.

35 Specifically, the compounds have utility as drugs for the

treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

5 Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described
10 by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay
15 mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate
20 concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as
25 a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 15 μM , thereby confirming the utility of the compounds of the present
30 invention as effective Xa inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or
35 platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically

effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicylic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A₂-receptor antagonists and thromboxane-A₂-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boro peptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boro peptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α -aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiuronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boro peptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boro peptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby

incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

5 Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side
10 effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a
15 commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay
20 was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

25 The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the
30 compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but no compound of the present invention, then one would conclude factor Xa was present.

35 Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations);

pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

10 The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the
15 recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug
20 required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per
25 day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single
30 daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin
35 patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol,

polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled
5 release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacylates, and crosslinked or amphipathic block
10 copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will
15 ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like.
20 Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the
25 tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous
30 dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if
35 necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition,

parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in
5 Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

10 Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams
15 magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into
20 gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so
25 that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase
30 palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The
35 solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

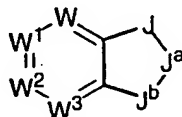
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the

scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

**WHAT IS CLAIMED AS NEW AND DESIRED TO BE SECURED BY LETTER
PATENT OF UNITED STATES IS:**

1. A compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein:

one of W, W¹, W², and W³ is C-D and the remaining are C-R¹;

alternatively, W-W¹, W¹-W², or W²-W³ combine to form C(D^a)N and
the remaining are C-R¹;

D is selected from CN, C(=NR⁷)NR⁸R⁹, NHC(=NR⁷)NR⁸R⁹,
NR⁸CH(=NR⁷), C(O)NR⁸R⁹, and (CH₂)_tNR⁸R⁹;

D^a is NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, or C₁₋₃ alkoxy;

J is selected from N(Z-A-B) and CR(Z-A-B); and

J^a and J^b together are selected from CONHCR^eR^f, SO₂NHCR^eR^f,
(CR^aR^b)_qSO₂NR^d, and (CR^aR^b)_bCOCO(CR^eR^f)_c, wherein b+c=0 or
1;

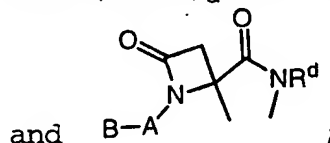
alternatively, J and J^a together are selected from
CON(Z-A-B)(CR^cR^b)_q and N(Z-A-B)Q(R^cR^b)_a; and

J^b is selected from NR^d, O, and CR^eR^f;

Q is CO or CS;

alternatively, J, J^a and J^b together are selected from
CR(Z-A-B)(CR^aR^b)_aQNR^d, CR(Z-A-B)(CR^aR^b)_dC(O)O,
CR(Z-A-B)NHCOCR^eR^f, CR(Z-A-B)NHSO₂CR^eR^f,

$N(Z-A-B)(CR^aR^b)_aQNR^d$, $N(Z-A-B)(CR^aR^b)C(O)O$,
 $N(Z-A-B)SO_2(CR^cR^b)_aCR^eR^f$, $N(Z-A-B)SO_2(CR^cR^b)_aNR^d$,
 $CON(Z-A-B)CR^eR^f$, $CONR^b(CR^cR^b)_aN(Z-A-B)$,



5

R is selected from H, C₁₋₆ alkyl, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, OH, C₁₋₆ alkoxy, C₁₋₆ alkoxy-C₁₋₄ alkyl, (CH₂)_tNR⁸R⁹, 5-6 membered aromatic heterocyclyl-C₁₋₄ alkyl, and aryl-C₁₋₄ alkyl, wherein the aromatic heterocyclyl and aryl groups are substituted with 0-1 R⁴;

10

R^a is selected from H, C₁₋₆ alkyl, C(O)R^{2b}, 5-6 membered aromatic heterocyclyl-C₁₋₄ alkyl, and aryl-C₁₋₄ alkyl, wherein the aromatic heterocyclyl and aryl groups are substituted with 0-1 R⁴;

15

R^b is H or C₁₋₂ alkyl;

R^c is selected from H, C₁₋₆ alkyl, C(O)R^{2b}, S(O)_pR^{2b}, BO₂H₂, 5-6 membered aromatic heterocyclyl-C₁₋₄ alkyl, and aryl-C₁₋₄ alkyl, wherein the aromatic heterocyclyl and aryl groups are substituted with 0-1 R⁴;

20

R^d is selected from H, OH, NH₂, C₁₋₂ alkyl, and C₁₋₂ alkyl-OH, alternatively, R^c and R^d, when attached to adjacent atoms, together form a double bond;

25

R^e is selected from H, OH, NH₂, C₁₋₂ alkyl, and C₁₋₂ alkyl-OH, alternatively, R^c and R^e, when attached to adjacent atoms, together form a double bond;

30

R^f is H or C₁₋₂ alkyl;

35

Z is selected from a bond, C₁₋₄ alkylene, (CH₂)_rO(CH₂)_r,
 (CH₂)_rNR³(CH₂)_r, (CH₂)_rC(O)(CH₂)_r, (CH₂)_rC(O)O(CH₂)_r,
 (CH₂)_rOC(O)(CH₂)_r, (CH₂)_rC(O)NR³(CH₂)_r,
 (CH₂)_rNR³C(O)(CH₂)_r, (CH₂)_rOC(O)O(CH₂)_r,
 5 (CH₂)_rOC(O)NR³(CH₂)_r, (CH₂)_rNR³C(O)O(CH₂)_r,
 (CH₂)_rNR³C(O)NR³(CH₂)_r, (CH₂)_rS(O)_p(CH₂)_r,
 (CH₂)_rSO₂NR³(CH₂)_r, (CH₂)_rNR³SO₂(CH₂)_r, and
 (CH₂)_rNR³SO₂NR³(CH₂)_r, provided that Z does not form a
 N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with the groups
 10 to which it is attached;

R¹, at each occurrence, is selected from H, F, Cl, Br, I,
 (CF₂)_rCF₃, OR², NR²R^{2a}, C(O)R^{2b}, (CF₂)_rCO₂R², S(O)₂R^{2b},
 NR²C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, C₃₋₆ carbocyclic residue
 15 substituted with 0-2 R⁴, and 5-10 membered heterocyclic
 system containing from 1-4 heteroatoms selected from the
 group consisting of N, O, and S and substituted with 0-2
 R⁴;

20 R^{1'}, at each occurrence, is selected from H, C₁₋₃ alkyl, F, Cl,
 Br, I, -CN, -CHO, (CF₂)_rCF₃, (CH₂)_rOR², NR²R^{2a}, C(O)R^{2c},
 OC(O)R², (CF₂)_rCO₂R^{2c}, S(O)_pR^{2b}, NR²(CH₂)_rOR²,
 CH(=NR^{2c})NR²R^{2a}, NR²C(O)R^{2b}, NR²C(O)NHR^{2b}, NR²C(O)₂R^{2a},
 OC(O)NR^{2a}R^{2b}, C(O)NR²R^{2a}, C(O)NR²(CH₂)_rOR², SO₂NR²R^{2a},
 25 NR²SO₂R^{2b}, C₃₋₆ carbocyclic residue substituted with 0-2
 R^{4b}, and 5-10 membered heterocyclic system containing from
 1-4 heteroatoms selected from the group consisting of N,
 O, and S substituted with 0-2 R^{4b};

30 R^{1''}, at each occurrence, is selected from H, CH(CH₂OR²)₂,
 C(O)R^{2c}, C(O)NR²R^{2a}, S(O)R^{2b}, S(O)₂R^{2b}, and SO₂NR²R^{2a};

R², at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl,
 benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b},
 35 and 5-6 membered heterocyclic system containing from 1-4
 heteroatoms selected from the group consisting of N, O,
 and S and substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{4b};

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^{2b} is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

A is selected from:
C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R⁴;

B is selected from: H, Y, and X-Y;

X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -C(=NR¹)-, -CR²(NR¹"R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O), -S(O)_p-, -S(O)_pCR²R^{2a}-,
 5 -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and
 10 -OCR²R^{2a}-;

Y is selected from:

(CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,
 15 C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, CH(=NR²)NR²R^{2a}, CH(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, C(O)NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄
 20 alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, NCH₂R¹", OCH₂R¹", SCH₂R¹", N(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and S(CH₂)₂(CH₂)_tR^{1'};

alternatively, one R⁴ is a 5-6 membered aromatic heterocycle
 30 containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR², (CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rNR²R^{2b}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, C(O)NH(CH₂)₂NR²R^{2a}, NR²C(O)NR²R^{2a}, CH(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a},
 35

$\text{NR}^2\text{SO}_2\text{-C}_{1-4}$ alkyl, $\text{C}(\text{O})\text{NHSO}_2\text{-C}_{1-4}$ alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$, $\text{S}(\text{O})_{\text{p}}\text{R}^5$,
and $(\text{CF}_2)_{\text{r}}\text{CF}_3$;

alternatively, one $\text{R}^{4\text{a}}$ is a 5-6 membered aromatic heterocycle
5 containing from 1-4 heteroatoms selected from the group
consisting of N, O, and S;

$\text{R}^{4\text{b}}$, at each occurrence, is selected from H, =O, $(\text{CH}_2)_{\text{r}}\text{OR}^3$, F,
Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(\text{CH}_2)_{\text{r}}\text{NR}^3\text{R}^{3\text{a}}$,
10 $(\text{CH}_2)_{\text{r}}\text{C}(\text{O})\text{R}^3$, $(\text{CH}_2)_{\text{r}}\text{C}(\text{O})\text{OR}^{3\text{c}}$, $\text{NR}^3\text{C}(\text{O})\text{R}^{3\text{a}}$, $\text{C}(\text{O})\text{NR}^3\text{R}^{3\text{a}}$,
 $\text{NR}^3\text{C}(\text{O})\text{NR}^3\text{R}^{3\text{a}}$, $\text{CH}(=\text{NR}^3)\text{NR}^3\text{R}^{3\text{a}}$, $\text{NH}^3\text{C}(=\text{NR}^3)\text{NR}^3\text{R}^{3\text{a}}$, $\text{SO}_2\text{NR}^3\text{R}^{3\text{a}}$,
 $\text{NR}^3\text{SO}_2\text{NR}^3\text{R}^{3\text{a}}$, $\text{NR}^3\text{SO}_2\text{-C}_{1-4}$ alkyl, $\text{NR}^3\text{SO}_2\text{CF}_3$, $\text{NR}^3\text{SO}_2\text{-phenyl}$,
 $\text{S}(\text{O})_{\text{p}}\text{CF}_3$, $\text{S}(\text{O})_{\text{p}}\text{-C}_{1-4}$ alkyl, $\text{S}(\text{O})_{\text{p}}\text{-phenyl}$, and $(\text{CF}_2)_{\text{r}}\text{CF}_3$;

15 R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl,
phenyl substituted with 0-2 R^6 , and benzyl substituted
with 0-2 R^6 ;

R^6 , at each occurrence, is selected from H, OH, $(\text{CH}_2)_{\text{r}}\text{OR}^2$, F,
20 Cl, Br, I, C_{1-4} alkyl, CN, NO_2 , $(\text{CH}_2)_{\text{r}}\text{NR}^2\text{R}^{2\text{a}}$, $(\text{CH}_2)_{\text{r}}\text{C}(\text{O})\text{R}^{2\text{b}}$,
 $\text{NR}^2\text{C}(\text{O})\text{R}^{2\text{b}}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2\text{a}}$, $\text{CH}(=\text{NH})\text{NH}_2$, $\text{NHC}(=\text{NH})\text{NH}_2$,
 $\text{SO}_2\text{NR}^2\text{R}^{2\text{a}}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2\text{a}}$, and $\text{NR}^2\text{SO}_2\text{C}_{1-4}$ alkyl;

R^7 , at each occurrence, is selected from H, OH, C_{1-6} alkyl,
25 C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, C_{6-10}
aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl,
 C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10}
arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6}
alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4}
30 alkoxycarbonyl;

R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and
 $(\text{CH}_2)_{\text{n}}\text{-phenyl}$;

35 R^9 , at each occurrence, is selected from H, C_{1-6} alkyl and
 $(\text{CH}_2)_{\text{n}}\text{-phenyl}$;

a, at each occurrence, is selected from 0, 1, and 2;

d, at each occurrence, is selected from 0 and 1;

n, at each occurrence, is selected from 0, 1, 2, and 3;

5

m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

10 q, at each occurrence, is selected from 1 and 2;

r, at each occurrence, is selected from 0, 1, and 2;

s, at each occurrence, is selected from 0, 1, and 2; and,

15

t, at each occurrence, is selected from 0 and 1;

provided that A-B is other than benzyl-thiazolidin-2,4-dione.

20

2. A compound according to Claim 1, wherein;

one of W, W¹, W², and W³ is C-D and the remaining are C-R¹;

25 J is selected from N(Z-A-B) and CR(Z-A-B); and

J^a and J^b together are selected from CONHCR^{eR^f}, SO₂NHCR^{eR^f},
(CR^{aR^b})_qSO₂NR^d, and (CR^{aR^b})_bCOCO(CR^{eR^f})_c, wherein b+c=0 or
1;

30

alternatively, J and J^a together are selected from
CON(Z-A-B)(CR^{cR^b}) and N(Z-A-B)Q(R^{cR^b})_a; and

J^b is selected from NR^d, O, and CR^{eR^f};

35

Q is CO;

alternatively, J, J^a and J^b together are selected from

CR(Z-A-B)(CR^aR^b)_aQNR^d, CR(Z-A-B)(CR^aR^b)_aC(O)O,

CR(Z-A-B)NHCOCRe^f, CR(Z-A-B)NHSO₂CR^eR^f,

N(Z-A-B)(CR^aR^b)_aQNR^d, N(Z-A-B)(CR^aR^b)C(O)O,

5 N(Z-A-B)SO₂(CR^cR^b)_aCR^eR^f, N(Z-A-B)SO₂(CR^cR^b)_aNR^d,

CON(Z-A-B)CR^eR^f, and CONR^b(CR^cR^b)_aN(Z-A-B);

Z is selected from a CH₂O, OCH₂, CH₂NH, NHCH₂, CH₂C(O),

C(O)CH₂, C(O)NH, C(O)NH, CH₂S(O)₂, S(O)₂(CH₂), SO₂NH, and

10 SO₂NH;

B is selected from: Y, X-Y, and NR²R^{2a};

Y is selected from one of the following carbocyclic and

15 heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl,

pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,

pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,

isothiazolyl, pyrazolyl, imidazolyl, oxadiazole,

20 thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-

oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-

thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-

thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-

triazole, 1,3,4-triazole, benzofuran, benzothiofuran,

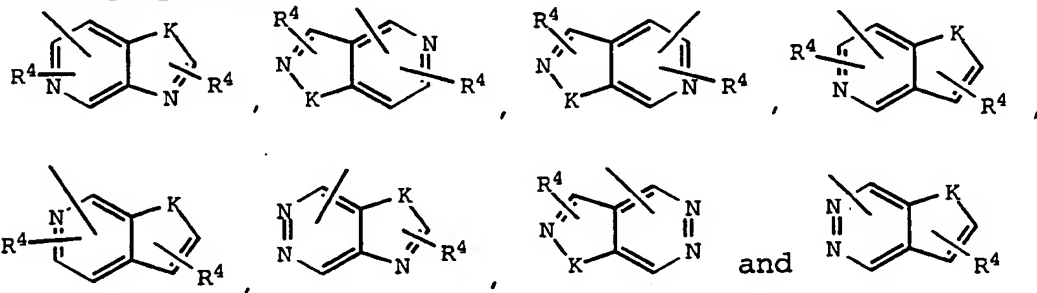
25 indole, benzimidazole, benzoxazole, benzthiazole,

indazole, benzisoxazole, benzisothiazole, and

isoindazole;

Y may also be selected from the following bicyclic heteroaryl

30 ring systems:

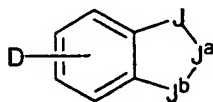


K is selected from O, S, NH, and N; and,

a, at each occurrence, is selected from 0 and 1.

5

3. A compound according to Claim 2, wherein;



Ia

10 or stereoisomer or pharmaceutically acceptable salt thereof,
wherein;

D is $C(=NR^7)NR^8R^9$;

15 J is selected from $N(Z-A-B)$ and $CR(Z-A-B)$; and

J^a and J^b together are selected from $CONHCR^eR^f$;

alternatively, J and J^a together are selected from
20 $CON(Z-A-B)(CR^cR^b)$ and $N(Z-A-B)Q(R^cR^b)_a$; and

J^b is selected from NR^d , O, and CR^eR^f ;

Q is CO;

25

alternatively, J, J^a and J^b together are selected from
 $CR(Z-A-B)(CR^aR^b)_aQNR^d$, $CR(Z-A-B)(CR^aR^b)_dC(O)O$,
 $N(Z-A-B)(CR^aR^b)_aQNR^d$, $N(Z-A-B)(CR^aR^b)C(O)O$,
 $CON(Z-A-B)CR^eR^f$, and $CONR^b(CR^cR^b)_aN(Z-A-B)$;

30

A is selected from:

piperidinyl,

piperazinyl,

C₅₋₆ carbocyclic residue substituted with 0-2 R^4 , and

5-6 membered heteroaryl containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-2 R⁴; and,

5 B is selected from: Y and X-Y.

4. A compound according to Claim 3, wherein;

10 J and J^a together are N(Z-A-B)C(O); and

J^b is selected from NR^d, O, and CR^eR^f;

alternatively, J, J^a and J^b together are CR(Z-A-B)C(O)NR^d; and,
15

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};
phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, benzimidazole, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, and 1,3,4-triazole.
20
25

5. A compound according to Claim 1, wherein the compound
30 is selected from:

1N-(2'-Aminosulfonyl-[1,1']biphenylamino)carbonylmethyl-6-amidinobenzimidazolinone;

35 1N-(2'-Aminosulfonyl-[1,1']biphenylamino)-carbonylmethyl-5-amidinobenzimidazolinone;

- 1N-[4'-(p-chlorophenyl)thiazolyl-2'-amino)carbonylmethyl-6-amidinobenzimidazolinone;
- 5 5-Amidino-1N-(1'N-(4'-benzylpiperidino)carbonylmethyl)benzimidazolinone;
- 1N-(2'-Aminosulfonyl-[1,1']biphenylamino)carbonylmethyl-3N- β -hydroxyethylene-6-amidinobenzimidazolinone;
- 10 1N-(1'N-(2'-aminosulfonyl-[1,1']-biphenylamino)carbonylmethyl)-6-amidinobenzoxazolinone;
- 1N-(N-p-(4'-oxazolyl)phenylamino)carbonylmethyl-6-amidino-benzoxazolinone;
- 15 1N-(1'N-(4'N-benzylsulfonylpiperazino)carbonylmethyl-6-amidino-benzoxazolinone;
- 7-amidino-1N-(4'-bromophenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one;
- 20 7-amidino-1N-(3'-amino-[1,1']biphenyl)carbonyl-methyl-3,4-dihydroquinoxalin-2(1H)-one;
- 25 7-amidino-1N-(4'-fluoro-[1,1']biphenyl)carbonyl-methyl-3,4-dihydroquinoxalin-2(1H)-one;
- 7-amidino-1N-[1,1']-biphenylcarbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one;
- 30 7-amidino-1N-(2'-tert-butylsulfonamido-[1,1']biphenyl)carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one;
- 35 7-amidino-1N-(2'-sulfonamido-[1,1']-biphenyl)-carbonylmethyl-3,4-dihydroquinoxalin-2(1H)-one;

- 1N-(2'-aminosulfonyl-[1,1']biphenylamino)carbonyl-methyl-7-
amidino-3,4-dihydroquinoxalin-2(1H)-one;
- 5 6-amidino-1N-[1,1']-biphenyl)carbonylmethyl-3,4-
dihydroquinoxalin-2(1H)-one;
- 1N-[1,1']Biphenylcarbonyl)ethyl-6-amidinobenzoxazolinone;
- 10 1-([1,1']-Biphenylcarbonyl)ethyl-6-amidino-3N-
methylbenzimidazolinone;
- 1-([1,1']-biphenylcarbonyl)ethyl-6-amidinobenzimidazolinone;
- 15 1N-(4-Bromophenylcarbonyl)ethyl-6-amidinobenzoxazolinone;
- 1N-[4-(2-Aminosulfonylphenyl)pyridin-2-yl]aminocarbonylmethyl-
6-amidinobenzoxazolinone;
- 20 1N-(4-Morpholinosulfonamidophenyl)aminocarbonylmethyl-6-
amidinobenzoxazolinone;
- 2-[3-(3-methoxy-(2'-aminosulfonyl-[1,1']biphenyl-1-
aminocarbonyl)methyl)-5-amidino-2-indolinone;
- 25 2-[3-(3-amino-(2'-aminosulfonyl-[1,1']-
biphenylaminocarbonyl)methyl)-5-amidino-2-indolinone;
- 2-[3-(3-hydroxy-(2'-aminosulfonyl-[1,1']-
biphenylaminocarbonyl)methyl)-5-amidino-2-indolinone;
- 30 2-[3-(3'-hydroxy-(2-chloro-(2'-aminosulfonyl)-[1,1']-
biphenylaminocarbonyl)methyl)-5-amidino-2-indolinone;
- 2-[3-(3'-amino-(2-chloro-(2'-aminosulfonyl)-[1,1']-
35 biphenylaminocarbonyl)methyl)-5-amidino-2-indolinone;
- 2-(3-(2-chloro-(2'-aminosulfonyl)-[1,1']biphenyl-3'-
aminocarbonyl)methyl)-5-amidino-2-indolinone;

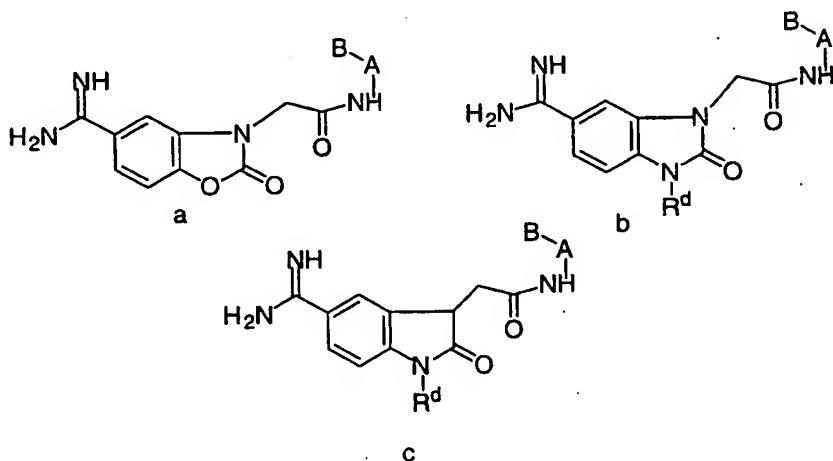
2-(3-(2-bromo-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl)-5-amidino-2-indolinone;

5 2-(3-(2-fluoro-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl)-5-amidino-2-indolinone; and,

2-(3-(2'-aminosulfonyl)-[1,1']biphenyl-3'-aminocarbonyl)methyl)-5-amidino-2-indolinone.

10

6. A compound according to Claim 1, wherein the compound is of the formula a, b, or c:



15

or stereoisomer or pharmaceutically acceptable salt form thereof.

20

7. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to one of Claims 1-6 or a pharmaceutically acceptable salt thereof.

25

8. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-6 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 98/18729

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D209/34 C07D241/44 C07D235/26 C07D263/58 A61K31/405
 A61K31/415 A61K31/42 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 587 134 A (DR KARL THOMAS GMBH) 16 March 1994 see the whole document ---	1,7
A	EP 0 540 051 A (DAICHI PHARMACEUTICAL CO.) 5 May 1993 cited in the application see the whole document ---	1,7
A	WO 97 30971 A (THE DU PONT MERCK PHARMACEUTICALS) 28 August 1997 see the whole document ---	1,7
A	WO 97 23212 A (THE DU PONT MERCK PHARMACEUTICALS) 3 July 1997 see the whole document ---	1,7
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

23 December 1998

Date of mailing of the International search report

07/01/1999

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INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 98/18729

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 06038 A (G. D. SEARLE & CO.) 2 March 1995 see the whole document ----	1,7
A	WO 96 38421 A (BERLEX LABORATORIES, INC.) 5 December 1996 see the whole document ----	1,7
A	WO 96 36639 A (G. D. SEARLE AND CO.) 21 November 1996 see the whole document -----	1,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/US 98/18729

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 587134	A	16-03-1994	DE 4230470 A	14-04-1994
			DE 4302052 A	28-07-1994
			DE 4309213 A	29-09-1994
			AU 4624993 A	24-03-1994
			BG 98103 A	15-07-1994
			CA 2105934 A	12-03-1994
			CN 1092769 A	28-09-1994
			CZ 9301881 A	16-11-1994
			FI 933942 A	12-03-1994
			HU 71496 A	28-11-1995
			JP 6263740 A	20-09-1994
			MX 9305566 A	31-05-1994
			NO 933248 A	14-03-1994
			NZ 248633 A	28-08-1995
			PL 300347 A	16-05-1994
			SK 94393 A	10-08-1994
			US 5681841 A	28-10-1997
			ZA 9306689 A	10-03-1995
EP 540051	A	05-05-1993	AT 136293 T	15-04-1996
			AU 666137 B	01-02-1996
			AU 2747092 A	06-05-1993
			CA 2081836 A	01-05-1993
			CN 1072677 A	02-06-1993
			CN 1168885 A	31-12-1997
			CN 1168886 A	31-12-1997
			CZ 284381 B	11-11-1998
			DE 69209615 D	09-05-1996
			DE 69209615 T	09-01-1997
			DK 540051 T	06-05-1996
			ES 2088073 T	01-08-1996
			FI 924932 A	01-05-1993
			GR 3019832 T	31-08-1996
			HR 921147 A	31-10-1995
			HU 65890 A	28-07-1994
			JP 10291931 A	04-11-1998
			JP 5208946 A	20-08-1993
			MX 9206295 A	01-08-1993
			NO 302948 B	11-05-1998
			NZ 244936 A	26-05-1995
			PL 170312 B	29-11-1996
			US 5576343 A	19-11-1996
			US 5620991 A	15-04-1997
			ZA 9208276 A	06-05-1993
WO 9730971	A	28-08-1997	AU 2056197 A	10-09-1997
WO 9723212	A	03-07-1997	AU 1335897 A	17-07-1997
			EP 0874629 A	04-11-1998
			HR 960597 A	30-04-1998
WO 9506038	A	02-03-1995	US 5430043 A	04-07-1995
			AT 170845 T	15-09-1998
			AU 7401994 A	21-03-1995
			CA 2168345 A	02-03-1995
			DE 69413237 D	15-10-1998
			EP 0715623 A	12-06-1996
			ES 2120728 T	01-11-1998

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/US 98/18729

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9506038 A		JP 9501692 T	18-02-1997
		US 5489594 A	06-02-1996
		ZA 9405836 A	04-08-1995
WO 9638421 A	05-12-1996	US 5612363 A	18-03-1997
		AU 5974696 A	18-12-1996
		CA 2221992 A	05-12-1996
		EP 0848708 A	24-06-1998
		US 5726173 A	10-03-1998
		US 5731308 A	24-03-1998
		US 5731311 A	24-03-1998
		US 5726198 A	10-03-1998
		US 5728697 A	17-03-1998
WO 9636639 A	21-11-1996	US 5674894 A	07-10-1997
		AU 696915 B	24-09-1998
		AU 5735996 A	29-11-1996
		CA 2220549 A	21-11-1996
		EP 0825994 A	04-03-1998
		NZ 307881 A	28-07-1998